

## TRICYCLIC COMPOUNDS USEFUL AS ANGIOTENSIN II AGONISTS

5 This application is a continuation-in-part of International Application PCT/GB02/02563, with an international filing date of January 4, 1990, now abandoned, the entirety of which is hereby incorporated by reference herein, which is a continuation-in-part of each of GB applications 0113129.1, filed May 31, 2001, 0121611.8, filed September 7, 2001, 0201794.5, filed January  
10 26, 2002, each of which is hereby incorporated by reference herein in its entirety, and which also claims the benefit of U.S. Provisional Application No. 60/350,959, filed January 25, 2002, the entirety of which is hereby incorporated by reference herein.

### 15 **Field of the Invention**

This invention relates to novel pharmaceutically-useful compounds, in particular compounds that are angiotensin II (AngII) agonists, more particularly agonists of the AngII type 2 receptor (hereinafter the AT2 receptor), and especially agonists that bind selectively to that receptor. The  
20 invention further relates to the use of such compounds as medicaments, to pharmaceutical compositions containing them, and to synthetic routes to their production.

### **Background and Prior Art**

25 The endogenous hormone AngII is a linear octapeptide (Asp<sup>1</sup>-Arg<sup>2</sup>-Val<sup>3</sup>-Tyr<sup>4</sup>-Ile<sup>5</sup>-His<sup>6</sup>-Pro<sup>7</sup>-Phe<sup>8</sup>), and is the active component of the renin-angiotensin system (RAS). It is produced by the sequential processing of the pro-hormone angiotensinogen by renin and angiotensin converting enzyme (ACE).

30 The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure, body fluid and electrolyte homeostasis. Ang II exerts these physiological actions in many organs including the kidneys, the adrenal glands, the heart, blood vessels, the brain, the gastrointestinal tract and the reproductive organs (de Gasparo *et al*, *Pharmacol. Rev.* (2000) **52**, 415-472).

35

Two main classes of AngII receptors have been identified, and designated as the type 1 receptor (hereinafter the AT1 receptor) and the AT2 receptor.

The AT1 receptor is expressed in most organs, and is believed to be responsible for the majority of the biological effects of AngII. The AT2 receptor is more prevalent than the AT1 receptor in fetal tissues, the adult ovaries, the adrenal medulla and the pancreas. An equal distribution is reported in the brain and uterus (Ardaillou, *J. Am. Soc. Nephrol.*, **10**, S30-39 (1999)).

Several studies in adult individuals appear to demonstrate that, in the modulation of the response following AngII stimulation, activation of the AT2 receptor has opposing effects to those mediated by the AT1 receptor.

The AT2 receptor has also been shown to be involved in apoptosis and inhibition of cell proliferation (see de Gasparo *et al, supra*). Further, it seems to play a role in blood pressure control. For example, it has been shown in transgenic mice lacking AT2 receptors that their blood pressure was elevated. Furthermore, it has been concluded that the AT2 receptor is involved in exploratory behaviour, pain sensitivity and thermoregulation.

The expression of AT2 receptors has also been shown to increase during pathological circumstances, such as vascular injury, wound healing and heart failure (see de Gasparo *et al, supra*).

The expected pharmacological effects of agonism of the AT2 receptor are described generally in de Gasparo *et al, supra*.

More recently, AT2 receptor agonists have been shown to be of potential utility in the treatment and/or prophylaxis of disorders of the alimentary tract, such as dyspepsia and irritable bowel syndrome, as well as multiple organ failure (see international patent application WO 99/43339).

AngII antagonists (which bind to the AT1 and/or AT2 receptors) have been disclosed in *inter alia* European patent applications EP 409 332, EP 512 675; international patent applications WO 94/27597, WO 94/02142, WO 95/23792  
5 and WO 94/03435; and US patent numbers 5,091,390, 5,177,074, 5,412,097, 5,250,521, 5,260,285, 5,376,666, 5,252,574, 5,312,820, 5,330,987, 5,166,206, 5,932,575 and 5,240,928. AngII agonists, and particularly AT2 receptor agonists, are not contemplated in any of these documents.

10 International patent application WO 00/68226 and US patent number 6,235,766 disclose compounds comprising substituted imidazolyl groups, which groups are attached, *via* a methylene bridge, to a phenylthiophene moiety, as agonists of angiotensin-(1-7) receptors. International patent application WO 01/44239 discloses biphenylsulfonamide compounds as  
15 combined angiotensin and endothelin receptor antagonists. The use of the compounds as Ang II receptor agonists is neither mentioned nor suggested in any of these documents.

US patent number 5,444,067 discloses compounds comprising a 5,7-dimethyl-  
20 2-ethylpyridinoimidazolyl group attached, *via* a methylene bridge, to a phenylthiophene moiety, as AT2 receptor agonists. The use of unsubstituted imidazole-containing compounds is neither mentioned nor suggested.

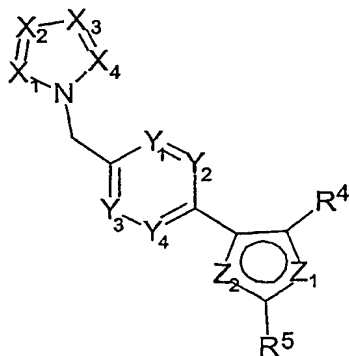
Peptide and non-peptide AT2 receptor agonists, unrelated structurally to  
25 those described herein, and potential uses thereof, have been disclosed in, for example, international patent applications WO 00/38676, WO 00/56345, WO 00/09144, WO 99/58140, WO 99/52540, WO 99/46285, WO 99/45945, WO 99/42122, WO 99/40107, WO 99/40106, WO 99/39743,

WO 99/26644, WO 98/33813, WO 00/02905 and WO 99/46285; US patent number 5,834,432; and Japanese patent application JP 143695.

However, there remains a need for effective and/or selective AT<sub>2</sub> receptor agonists, which are expected to find utility in *inter alia* the above-mentioned conditions.

### Disclosure of the Invention

According to the invention there is provided a compound of formula I,



wherein

- one of X<sub>1</sub> and X<sub>2</sub> represents -N- and the other represents -C(R<sup>1</sup>)-;
- X<sub>3</sub> represents -N- or -C(R<sup>2</sup>)-;
- X<sub>4</sub> represents -N- or -C(R<sup>3</sup>)-;
- R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> independently represent H, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkoxy-C<sub>1-6</sub>-alkyl or halo;
- provided that, when X<sub>1</sub> represents -C(R<sup>1</sup>)-, X<sub>3</sub> represents -C(R<sup>2</sup>)- and X<sub>4</sub> represents -C(R<sup>3</sup>)-, then R<sup>1</sup> represents H;
- Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub> and Y<sub>4</sub> independently represent -CH- or -CF-;
- Z<sub>1</sub> represents -CH-, -O-, -S-, -N- or -CH=CH-;

$Z_2$  represents  $-\text{CH}-$ ,  $-\text{O}-$ ,  $-\text{S}-$  or  $-\text{N}-$ ;

provided that:

- (a)  $Z_1$  and  $Z_2$  are not the same;
- (b) when  $Z_1$  represents  $-\text{CH}=\text{CH}-$ , then  $Z_2$  may only represent  $-\text{CH}-$  or  $-\text{N}-$ ; and
- (c) other than in the specific case in which  $Z_1$  represents  $-\text{CH}=\text{CH}-$ , and  $Z_2$  represents  $-\text{CH}-$ , when one  $Z_1$  and  $Z_2$  represents  $-\text{CH}-$ , then the other represents  $-\text{O}-$  or  $-\text{S}-$ ;

$R^4$  represents  $-\text{S}(\text{O})_2\text{N}(\text{H})\text{C}(\text{O})\text{R}^6$ ,  $-\text{S}(\text{O})_2\text{N}(\text{H})\text{S}(\text{O})_2\text{R}^6$ ,  $-\text{C}(\text{O})\text{N}(\text{H})\text{S}(\text{O})_2\text{R}^6$ ,

or, when  $Z_1$  represents  $-\text{CH}=\text{CH}-$ ,  $R^4$  may represent  $-\text{N}(\text{H})\text{S}(\text{O})_2\text{N}(\text{H})\text{C}(\text{O})\text{R}^7$  or  $-\text{N}(\text{H})\text{C}(\text{O})\text{N}(\text{H})\text{S}(\text{O})_2\text{R}^7$ ;

$R^5$  represents  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{C}_{1-6}$  alkoxy- $\text{C}_{1-6}$ -alkyl or di- $\text{C}_{1-3}$ -alkylamino- $\text{C}_{1-4}$ -alkyl;

$R^6$  represents  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{C}_{1-6}$  alkoxy- $\text{C}_{1-6}$ -alkyl,

$\text{C}_{1-3}$  alkoxy- $\text{C}_{1-6}$ -alkoxy,  $\text{C}_{1-6}$  alkylamino or di- $\text{C}_{1-6}$  alkylamino; and

$R^7$  represents  $\text{C}_{1-6}$  alkyl,

or a pharmaceutically-acceptable salt thereof,

which compounds and salts are referred to together hereinafter as "the compounds of the invention".

Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of the invention with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo* or by freeze-drying). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

Unless otherwise specified, alkyl groups, and the alkyl parts of alkoxy, alkoxyalkyl, alkoxyalkoxy, alkylamino and alkylaminoalkyl groups, as defined herein may be straight-chain or, when there is a sufficient number  
 5 (i.e. a minimum of three) of carbon atoms, be branched-chain, and/or cyclic. Further, when there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic/acyclic. Such alkyl groups, and alkyl parts of alkoxy, alkoxyalkyl, alkoxyalkoxy, alkylamino and alkylaminoalkyl groups, may also be saturated or, when there is a  
 10 sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated. Unless otherwise specified, such groups may also be substituted by one or more halo, and especially fluoro, atoms.

For the avoidance of doubt, alkoxy and alkoxyalkoxy groups are attached to  
 15 the rest of the molecule *via* the oxygen atom in that group, alkylamino groups are attached to the rest of the molecule *via* the nitrogen atom of the amino part of that group and alkylaminoalkyl and alkoxyalkyl groups are attached to the rest of the molecule *via* the alkyl part of that group.

20 The term "halo", when used herein, includes fluoro, chloro, bromo and iodo.

Preferred ring systems comprising the substituents  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  include phenyl groups. For the avoidance of doubt, the ring systems in compounds of formula I that comprise the groups  $Z_1$  and  $Z_2$ , are aromatic in  
 25 nature. In some instances, for example in cases where one or more of  $Z_1$  and  $Z_2$  represent  $-CH-$  or  $-N-$  the skilled person will appreciate that an additional H atom may necessarily be bonded to that CH group or N atom, in order to ensure that the rules of valency are adhered to. Preferred ring systems comprising  $Z_1$  and  $Z_2$  include oxazole groups, thiazole groups,  
 30 phenyl groups, pyridinyl groups, thiophenyl groups and furanyl groups.

In this respect, compounds of the invention may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

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Compounds of the invention also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers  
 10 may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by  
 15 derivatisation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (e.g. HPLC, chromatography over silica). All stereoisomers are included within the scope of the invention.

20 Preferred compounds of the invention include those in which:

- (i) when  $X_1$  represents  $-C(R^1)-$ , then:
  - (a)  $X_3$  represents  $-C(R^2)-$  and  $X_4$  represents  $-N-$ ;
  - (b)  $X_3$  and  $X_4$  both represent  $N$ ; or
  - (c)  $X_3$  represents  $-C(R^2)-$  and  $X_4$  represents  $-C(R^3)-$ ; or
- 25 (ii) when  $X_1$  represents  $-N-$ , then
  - (a)  $X_3$  represents  $-N-$ ; or
  - (b)  $X_3$  represents  $-C(R^2)-$  and  $X_4$  represents  $-C(R^3)-$ .

In case (i)(a) above, it is further preferred that  $R^1$  represents  $H$ .

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In case (ii)(a) above, when  $X_4$  represents  $-C(R^3)-$ , it is further preferred that  $R^3$  represents H.

Preferred compounds of formula I include those in which:

- 5  $R^1$  represents  $C_{1-3}$  alkyl, such as ethyl,  $-CF_3$  or, especially, H;
  - $R^2$  represents  $C_{1-3}$  alkyl, such as methyl, halo, or, especially, H;
  - $R^3$  represents  $C_{1-3}$  alkyl, halo or, especially, H;
  - $Y_1, Y_2, Y_3$  and  $Y_4$  all represent  $-CH-$ ;
  - $Z_1$  represents  $-S-$  or  $-CH=CH-$ ;
  - 10  $Z_2$  represents  $-CH-$ ;
  - $R^4$  represents  $S(O)_2N(H)C(O)R^6$ ;
  - $R^5$  represents *n*-butyl or, particularly, *iso*-butyl;
  - $R^6$  represents *n*-butoxymethyl, *iso*-butoxy and especially, *n*-butoxy.
- 15 Preferred ring systems comprising the substituents  $X_1, X_2, X_3$  and  $X_4$  include pyrazole groups, imidazole groups, 1,2,4-triazole groups and tetrazole groups.

Compounds of the invention that may be mentioned include those in which,  
 20 when  $X_1, X_3$  and  $X_4$  all represent  $-CH-$ ,  $Y_1, Y_2, Y_3$  and  $Y_4$  all represent  $-CH-$ ,  $Z_1$  represents  $-CH=CH-$  or, particularly,  $-S-$ ,  $Z_2$  represents  $-CH-$  and  $R^5$  represents *n*-butyl or, particularly, *iso*-butyl, then  $R^4$  represents  $-S(O)_2N(H)C(O)R^6$ , in which  $R^6$  represents  $-O$ -*iso*-propyl (i.e. *iso*-propoxy),  $-O$ -*iso*-butyl (i.e. *iso*-butoxy),  $-CH_2-O$ -*n*-butyl (i.e. *n*-butoxymethyl) or,  
 25 particularly,  $-O$ -*n*-butyl (i.e. *n*-butoxy).

Compounds of the invention that may further be mentioned include those in which, when  $X_1, X_3$  and  $X_4$  all represent  $-CH-$ ,  $Y_1, Y_2, Y_3$  and  $Y_4$  all represent  $-CH-$ ,  $Z_1$  represents  $-CH=CH-$  or  $-S-$ ,  $Z_2$  represents  $-CH-$  and  $R^5$   
 30 represents *n*-butyl or *iso*-butyl, then  $R^4$  does not represent



$-\text{S}(\text{O})_2\text{N}(\text{H})\text{C}(\text{O})\text{R}^6$ , in which  $\text{R}^6$  represents  $-\text{O}-\text{iso}-\text{propyl}$ ,  $-\text{O}-\text{iso}-\text{butyl}$ ,  $-\text{CH}_2-\text{O}-n-\text{butyl}$  or  $-\text{O}-n-\text{butyl}$ .

Further compounds of the invention that may be mentioned include those in which:

$\text{R}^4$  does not represent  $-\text{S}(\text{O})_2\text{N}(\text{H})\text{S}(\text{O})_2\text{R}^6$ ;

$\text{R}^5$  does not represent di- $\text{C}_{1-3}$  alkylamino- $\text{C}_{1-4}$ -alkyl;

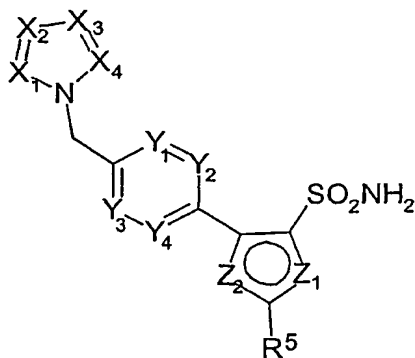
$\text{R}^6$  does not represent  $\text{C}_{1-3}$  alkoxy- $\text{C}_{1-6}$  alkoxy.

More preferred compounds of the invention include the compounds of the examples described hereinafter.

Compounds of formula I may be made in accordance with techniques well known to those skilled in the art, for example as described hereinafter.

According to a further aspect of the invention there is provided a process for the preparation of a compound of formula I, which process comprises:

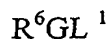
(i) for compounds of formula I in which  $\text{R}^4$  represents  $-\text{S}(\text{O})_2\text{N}(\text{H})\text{C}(\text{O})\text{R}^6$  or  $-\text{S}(\text{O})_2\text{N}(\text{H})\text{S}(\text{O})_2\text{R}^6$ , and  $\text{R}^6$  is as hereinbefore defined, reaction of a compound of formula II,



II

wherein  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$ ,  $Z_1$ ,  $Z_2$  and  $R^5$  are as hereinbefore defined with a compound of formula III,

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III

wherein G represents C(O) or S(O)<sub>2</sub> (as appropriate), L<sup>1</sup> represents a suitable leaving group, such as halo (e.g. chloro or bromo) and R<sup>6</sup> is as hereinbefore defined, for example at around room temperature or above  
 10 (e.g. up to 60-70°C) in the presence of a suitable base (e.g. pyrrolidinopyridine, pyridine, triethylamine, tributylamine, trimethylamine, dimethylaminopyridine, di-*iso*-propylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium hydroxide, or mixtures thereof) and an appropriate solvent (e.g. pyridine, dichloromethane, chloroform, tetrahydrofuran,  
 15 dimethylformamide, trifluoromethylbenzene or triethylamine). Preferred base/solvent systems for compounds of formula III in which G is C(O) include pyrrolidinopyridine/pyridine, pyrrolidinopyridine/triethylamine, dimethylaminopyridine/pyridine or dimethylaminopyridine/triethylamine. Preferred base/solvent systems for compounds of formula III in which G is  
 20 S(O)<sub>2</sub> include NaOH/THF;

(ii) for compounds of formula I in which R<sup>4</sup> represents -S(O)<sub>2</sub>N(H)C(O)R<sup>6</sup> and R<sup>6</sup> represents C<sub>1-6</sub> alkoxy-C<sub>1-6</sub>-alkyl, coupling of a compound of formula II as hereinbefore defined with a compound of formula IV,

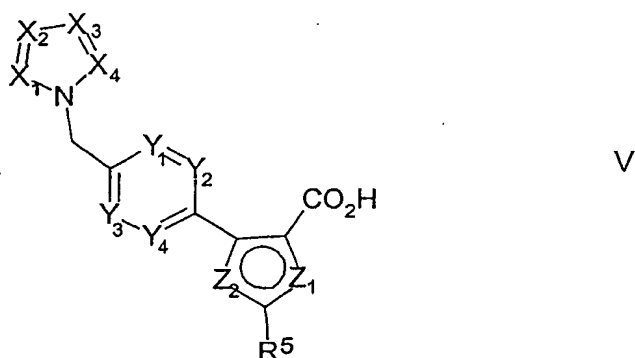
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IV

wherein R<sup>6a</sup> represents C<sub>1-6</sub> alkoxy-C<sub>1-6</sub>-alkyl, for example under similar conditions to those described under process step (i) above, in the presence  
 30 of a suitable coupling reagent (e.g. 1,1'-carbonyl-diimidazole, N,N'-

- dicyclohexylcarbodiimide, N,N'-disuccinimidyl carbonate, benzotriazole-1-  
 yloxytris(dimethylamino)phosphoniumhexafluorophosphate, 2-(1H-  
 benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate,  
 benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate,  
 5 bromo-tris-pyrrolidinophosponium hexafluorophosphate or 2-(1H-  
 benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluorocarbonate), a  
 suitable base (as mentioned in process step (i) above) and an appropriate  
 solvent (as mentioned in process step (i) above);
- 10 (iii) for compounds of formula I in which  $R^4$  represents  $-C(O)N(H)S(O)_2R^6$   
 and  $R^6$  is as hereinbefore defined, coupling of a compound of formula V,



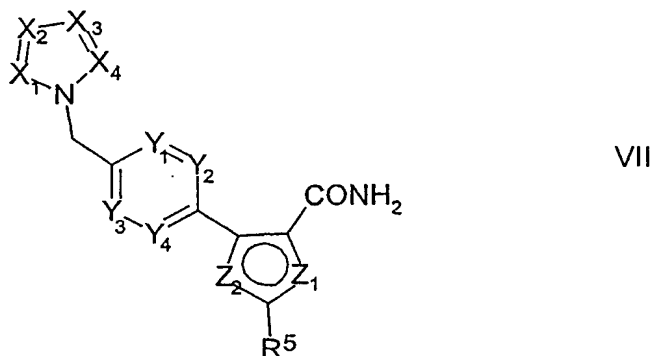
- 15 wherein  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$ ,  $Z_1$ ,  $Z_2$  and  $R^5$  are as hereinbefore  
 defined with a compound of formula VI,



- 20 wherein  $R^6$  is as hereinbefore defined, for example in the presence of a  
 suitable coupling reagent (such as those described in process step (ii)  
 hereinbefore), and under similar reaction conditions to those described

hereinbefore for preparation of compounds of formula I in which  $R^6$  represents  $C_{1-6}$  alkoxy- $C_{1-6}$ -alkyl;

- (iv) for compounds of formula I in which  $R^4$  represents  $-C(O)N(H)S(O)_2R^6$   
 5 and  $R^6$  is as hereinbefore defined, coupling of a compound of formula VII,

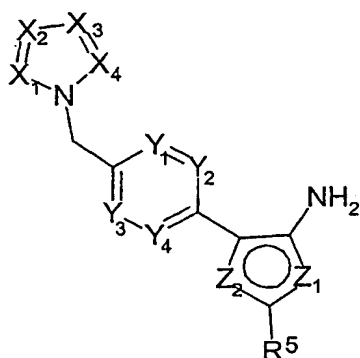


- wherein  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$ ,  $Z_1$ ,  $Z_2$  and  $R^5$  are as hereinbefore  
 10 defined with a compound of formula VIII,



- wherein  $R^6$  is as hereinbefore defined, for example at around  $50^\circ\text{C}$  in the  
 presence of a suitable base (e.g. sodium hydride) and an appropriate organic  
 15 solvent (e.g. THF);

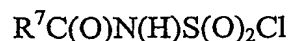
- (v) for compounds of formula I in which  $R^4$  represents  
 $-N(H)S(O)_2N(H)C(O)R^7$  and  $R^7$  is as hereinbefore defined, reaction of a  
 compound of formula IX,



IX

wherein  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$ ,  $Z_1$ ,  $Z_2$  and  $R^5$  are as hereinbefore defined with a compound of formula X,

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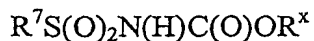


X

wherein  $R^7$  is as hereinbefore defined, for example at or around room temperature in the presence of a suitable base (e.g. sodium hydroxide or triethylamine) and a suitable organic solvent (e.g. benzene or dichloromethane);

(vi) for compounds of formula I in which  $R^4$  represents  $-N(H)C(O)N(H)S(O)_2R^7$  and  $R^7$  is as hereinbefore defined, reaction of a compound of formula IX as hereinbefore defined with a compound of formula XI,

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XI

wherein  $R^x$  represents  $C_{1-2}$  alkyl and  $R^7$  is as hereinbefore defined, for example at or around room temperature in the presence of a suitable organic solvent (e.g. dichloromethane);

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(vii) for compounds of formula I in which  $R^4$  represents  $-N(H)C(O)N(H)S(O)_2R^7$  and  $R^7$  is as hereinbefore defined, reaction of a compound of formula IX as hereinbefore defined with an isocyanate compound of formula XII,

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wherein  $R^7$  is as hereinbefore defined, for example at or around room temperature in the presence of a suitable organic solvent (e.g. dichloromethane);

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(viii) for compounds of formula I in which  $R^4$  represents  $-S(O)_2N(H)C(O)R^6$  and  $R^6$  represents  $C_{1-6}$  alkylamino, reaction of a compound of formula II as hereinbefore defined with an isocyanate compound of formula XIII,

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wherein  $R^{6b}$  is  $C_{1-6}$  alkyl, for example at or around room temperature in the presence of a suitable base (e.g. sodium hydroxide or potassium hydroxide and an appropriate organic solvent (e.g. acetone or acetonitrile); or

20

(ix) for compounds of formula I in which  $R^4$  represents  $-S(O)_2N(H)C(O)R^6$  and  $R^6$  represents di- $C_{1-6}$  alkylamino, reaction of a corresponding compound of formula I in which  $R^4$  represents  $-S(O)_2N(H)C(O)R^6$  and  $R^6$  represents  $C_{1-6}$  alkoxy with an amine of formula XIV,

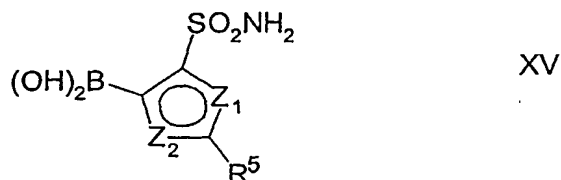
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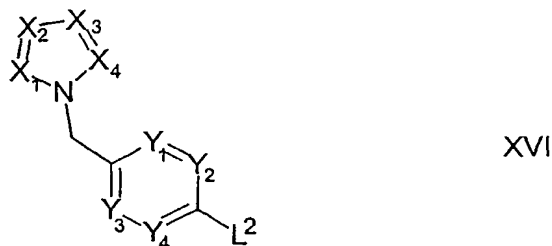
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wherein  $R^{6c}$  and  $R^{6d}$  independently represent  $C_{1-6}$  alkyl, for example at above room temperature (e.g. at between  $70^{\circ}\text{C}$  and  $100^{\circ}\text{C}$ ) in the presence of an appropriate organic solvent (e.g. toluene).

- 5 Compounds of formula II may be prepared by reaction of a compound of formula XV,



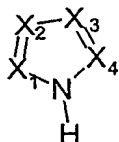
- 10 wherein  $R^5$ ,  $Z^1$  and  $Z^2$  are as hereinbefore defined, or a N-protected derivative thereof, with a compound of formula XVI,



- 15 wherein  $L^2$  represents a suitable leaving group, such as trimethylsulphonate, or halo, such as iodo or bromo, and  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  are as hereinbefore defined, for example in the presence of an appropriate coupling catalyst system (e.g. a palladium catalyst, such as  $\text{Pd}(\text{PPh}_3)_4$  or  $\text{Pd}(\text{OAc})_2/\text{ligand}$  (wherein the ligand may be, for example,  $\text{PPh}_3$ ,  $\text{P}(\text{o-Tol})_3$  or 1,1'-bis(diphenylphosphino)ferrocene)) and a suitable base (e.g. sodium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, triethylamine or di-*iso*-propylamine)), as well as a suitable solvent system (e.g. toluene, ethanol, dimethoxymethane, dimethylformamide, ethylene
- 20

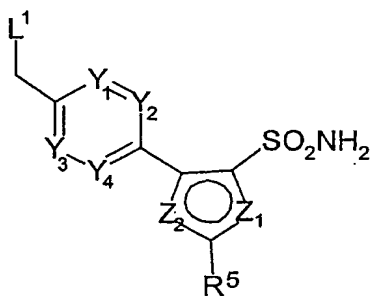
glycol dimethyl ether, water, dioxane or mixtures thereof). This reaction may be carried out at above room temperature (e.g. at the reflux temperature of the solvent system that is employed). If a protected version of a compound of formula XV is employed, this reaction may be followed by  
 5 deprotection of the SO<sub>2</sub>NH-group under standard conditions, for example as described hereinafter.

Compounds of formula II may alternatively be prepared by reaction of a compound of formula XVII,



XVII

wherein X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub> and X<sub>4</sub> are as hereinbefore defined with a compound of formula XVIII,



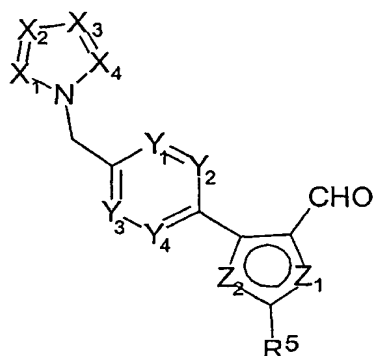
XVIII

wherein Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub>, Y<sub>4</sub>, Z<sub>1</sub>, Z<sub>2</sub>, R<sup>5</sup> and L<sup>1</sup> are as hereinbefore defined (L<sup>1</sup>, in particular, may represent bromo), or a N-protected derivative thereof, for  
 20 example at around or below room temperature in the presence of a suitable base (e.g. potassium hydroxide) and an appropriate organic solvent (e.g. DMSO). If a protected version of a compound of formula XVIII is



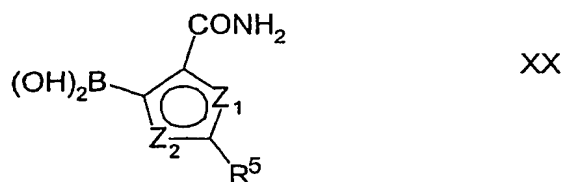
employed, this reaction may be followed by deprotection of the  $\text{SO}_2\text{NH}$ -group under standard conditions, for example as described hereinafter. Additionally, compounds of formula II in which  $\text{Z}_1$  is  $-\text{CH}=\text{CH}-$  and  $\text{Z}_2$  is  $-\text{CH}-$  may be prepared in this way, for example according, or analogously, to processes described in *inter alia* US patent number 5,312,820. Further, compounds of formula II in which  $\text{Z}_1$  is  $-\text{S}-$  and  $\text{Z}_2$  is  $-\text{CH}-$  may be prepared in this way for example according, or analogously, to processes described in *inter alia* UK patent application GB 2281298.

- 10 Compounds of formula V may be prepared by oxidation of a compound of formula XIX,

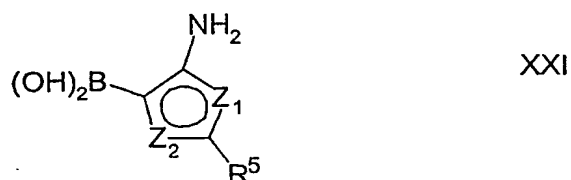


XIX

- 15 wherein  $\text{X}_1$ ,  $\text{X}_2$ ,  $\text{X}_3$ ,  $\text{X}_4$ ,  $\text{Y}_1$ ,  $\text{Y}_2$ ,  $\text{Y}_3$ ,  $\text{Y}_4$ ,  $\text{Z}_1$ ,  $\text{Z}_2$  and  $\text{R}^5$  are as hereinbefore defined, for example under standard oxidation conditions in the presence of a suitable oxidising agent, such as potassium permanganate or chromium (VI) oxide.
- 20 Compounds of formulae VII and IX may be prepared by reaction of a compound of formula XVI as hereinbefore defined with (in the case of a compound of formula VII) a compound of formula XX,



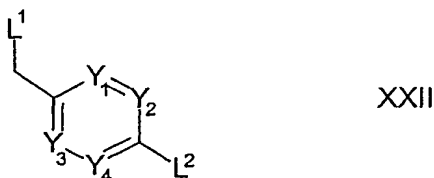
or (in the case of a compound of formula IX) a compound of formula XXI,



5

wherein, in both cases,  $Z_1$ ,  $Z_2$  and  $R^5$  are as hereinbefore defined, or N-protected derivatives thereof, for example under similar conditions to those described hereinbefore for preparation of compounds of formula II (first process). If protected versions of compounds of formulae XX and XXI are employed, these reactions may be followed by deprotection of the NH-group under standard conditions (e.g. acid hydrolysis).

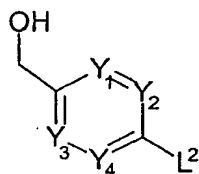
Compounds of formula XVI may be prepared by standard techniques, for example by way of reaction of a compound of formula XVII as hereinbefore defined with a compound of formula XXII,



wherein  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$ ,  $L^1$  and  $L^2$  are as hereinbefore defined, for example under similar conditions to those described hereinbefore in respect of preparation of compounds of formula II (second process).

- 5 Compounds of formula XVIII are known in the art. For example, they may be prepared according, or analogously, to processes described in *inter alia* US patent number 5,312,820, UK patent application GB 2281298, and/or by reaction of a compound of formula XV as hereinbefore defined with a compound of formula XXIII,

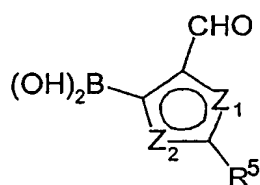
10



XXIII

- wherein  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$  and  $L^2$  are as hereinbefore defined, for example under similar conditions to those described hereinbefore in respect of preparation of compounds of formula II (first process), followed by conversion of the OH group in the resultant intermediate to an appropriate leaving group,  $L^1$  (e.g., in the case where  $L^1$  is bromo, conversion may be carried out by reaction with  $CBr_4$ , for example at or around room temperature in the presence of a base (e.g. triphenylphosphine) and a suitable organic solvent (e.g. DMF)).
- 15
- 20

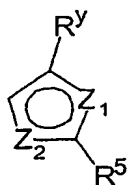
Compounds of formula XIX may be prepared by reaction of a compound of formula XVI as hereinbefore defined with a compound of formula XXIV,



XXIV

wherein  $Z_1$ ,  $Z_2$  and  $R^5$  are as hereinbefore defined, or a protected (at the aldehyde part) derivative thereof, for example under similar conditions to those described hereinbefore for preparation of compounds of formula II (first process). If a protected version of a compound of formula XXIV is employed, this reaction may be followed by deprotection of the CHO-group under standard conditions (e.g. acid hydrolysis).

- Compounds of formulae XV, XX, XXI and XXIV and protected derivatives thereof may be prepared by reaction of a corresponding compound of formula XXV,



XXV

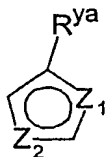
- wherein  $R^y$  represents  $-S(O)_2NH_2$ ,  $-C(O)NH_2$ ,  $-NH_2$  or  $-CHO$  (as appropriate) and  $R^5$ ,  $Z_1$  and  $Z_2$  are as hereinbefore defined, or an appropriate protected derivative thereof, with a reagent system that will enable the introduction of the  $-B(OH)_2$  into the appropriate ring system. Suitable reagent systems include trialkylborates (e.g. tri-*iso*-propylborate). Such reactions may be carried out, for example, at low temperature (e.g. between  $-100^\circ C$  and  $0^\circ C$ , e.g. between  $-80^\circ C$  (such as  $-78^\circ C$ ) and  $-10^\circ C$  (such as  $-20^\circ C$ )) in the presence of a suitable base (e.g. *n*-butyl lithium) and an

appropriate organic solvent (e.g. THF), followed by acid hydrolysis (e.g. in the presence of dilute HCl).

Compounds of formula XXV are available using known techniques. For  
5 example:

- (a) Compounds of formula XXV in which  $R^y$  represents  $-S(O)_2NH_2$ ,  $-C(O)NH_2$  or  $-CHO$ , and protected derivatives thereof, may be prepared by reaction of a compound of formula XXVI,

10



XXVI

wherein  $R^{ya}$  represents  $-S(O)_2NH_2$ ,  $-C(O)NH_2$  or  $-CHO$  and  $Z_1$  and  $Z_2$  are as hereinbefore defined, or a protected derivative thereof, with  
15 a compound of formula XXVII,

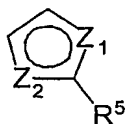


XXVII

wherein  $L^3$  represents a suitable leaving group (such as  
20 toluenesulphonate, benzenesulphonate, methanesulphonate or halo, such as bromo or iodo) and  $R^5$  is as hereinbefore defined, for example at below room temperature (e.g. between around  $-35^\circ\text{C}$  and around  $-85^\circ\text{C}$ ), in the presence of a suitable base (e.g. *n*-butyl lithium) and an appropriate solvent (e.g. THF).

25

- (b) Compounds of formula XXV in which  $R^y$  is  $-S(O)_2NH_2$  and N-protected derivatives thereof, may be prepared by reaction of an appropriate compound of formula XXVIII,



XXVIII

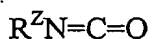
5

wherein  $R^5$ ,  $Z_1$  and  $Z_2$  are as hereinbefore defined with an appropriate reagent for introduction of a  $-S(O)_2NH_2$  group into the appropriate ring system (for example chlorosulphonic acid, or thionyl chloride in the presence of a suitable strong base (e.g. butyl lithium)), followed by reaction of the resultant intermediate with ammonia, or a protected derivative thereof (e.g. *tert*-butylamine), under conditions that are well known to those skilled in the art.

10

- (c) Certain protected derivatives (e.g. alkyl, such as  $C_{1-6}$  alkyl, for example *tert*-butyl, protected derivatives) of compounds of formula XXV in which  $R^y$  represents  $-C(O)NH_2$  may be prepared by reaction of a compound of formula XXVIII as hereinbefore defined, with a compound of formula XXIX,

20

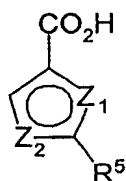


XXIX

25

wherein  $R^Z$  represents an appropriate protecting group, such as an alkyl group, including  $C_{1-6}$  alkyl, e.g. *tert*-butyl, for example at low temperature (e.g.  $-78^\circ C$  to around  $0^\circ C$ ), in the presence of a suitable base (e.g. *n*-butyl lithium) and an appropriate solvent (e.g. THF).

- (d) Certain protected derivatives (e.g. alkyl, such as C<sub>1-6</sub> alkyl, for example *tert*-butyl, protected derivatives) of compounds of formula XXV in which R<sup>y</sup> represents -C(O)NH<sub>2</sub> may also be prepared by reaction of a compound of formula XXX,



XXX

wherein R<sup>5</sup>, Z<sub>1</sub> and Z<sub>2</sub> are as hereinbefore defined with a protected (e.g. an (e.g. C<sub>1-6</sub>) alkyl, such as *tert*-butyl-protected) derivative of ammonia (e.g. *tert*-butylamine) under standard coupling conditions (see, for example, those described hereinbefore for preparation of compounds of formula I (process step (iii))). Compounds of formula XXX are known in the art or may be prepared by way of standard techniques, for example oxidation of a corresponding compound of formula XXV in which R<sup>y</sup> is -CHO e.g. under those conditions described hereinbefore for preparation of compounds of formula V.

- (e) Compounds of formula XXV in which R<sup>y</sup> is -CHO, Z<sub>1</sub> represents -CH=CH- and Z<sub>2</sub> represents -CH-, and protected derivatives thereof, may be prepared by reaction of a compound of formula XXVIII in which Z<sub>1</sub> represents -CH=CH- and Z<sub>2</sub> represents -CH- with an appropriate reagent system for the introduction of an aldehyde group into the benzene ring (e.g. TiCl<sub>4</sub>/CHCl<sub>3</sub>, SnCl<sub>4</sub>/CH<sub>2</sub>Cl<sub>2</sub> or 1,3,5,7-azaadamantane/TFA) under standard reaction conditions, followed by (if appropriate) protection of the resultant benzaldehyde under standard conditions.

- (f) Compounds of formula XXV in which  $R^y$  is  $-NH_2$ ,  $Z_1$  represents  $-CH=CH-$  and  $Z_2$  represents  $-CH-$ , and N-protected derivatives thereof, may be prepared by nitration of a compound of formula XXVIII in which  $Z_1$  represents  $-CH=CH-$  and  $Z_2$  represents  $-CH-$ ,  
5 followed by reduction of the resultant nitrobenzene and (if appropriate) protection of the resultant aminobenzene, all of which steps may be carried out under standard conditions.

Compounds of formulae III, IV, VI, VIII, X, XI, XII, XIII, XIV, XVII,  
10 XXII, XXIII, XXVI, XXVII, XXVIII and XXIX are either commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions.

15 Compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

It will be appreciated by those skilled in the art that, in the processes  
20 described above and hereinafter, the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups that it is desirable to protect include sulphonamido, amido, amino and aldehyde. Suitable protecting groups for sulphonamido, amido and amino include *tert*-butyloxycarbonyl, benzyloxycarbonyl, 2-  
25 trimethylsilylethoxycarbonyl (Teoc) or *tert*-butyl. Suitable protecting groups for aldehyde include alcohols, such as methanol or ethanol, and diols, such as 1,3-propanediol or, preferably, 1,2-ethanediol (so forming a cyclic acetal).

30



The protection and deprotection of functional groups may take place before or after a reaction in the above-mentioned schemes.

Protecting groups may be removed in accordance with techniques that are well known to those skilled in the art and as described hereinafter. For example, protected compounds/intermediates described herein may be converted chemically to unprotected compounds using standard deprotection techniques (e.g. using trifluoroacetic acid, sulfuric acid, toluenesulfonic acid or boron trichloride).

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This may negate, or render necessary, the need for protecting groups.

The type of chemistry involved will dictate the need, and type, of protecting groups as well as the sequence for accomplishing the synthesis.

The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by J W F McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 3<sup>rd</sup> edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

### Medical and Pharmaceutical Uses

Compounds of the invention are useful because they possess pharmacological activity. The compounds of the invention are therefore  
5 indicated as pharmaceuticals.

According to a further aspect of the invention there is thus provided the compounds of the invention for use as pharmaceuticals.

10 In particular, compounds of the invention are agonists of AngII, more particularly, are agonists of the AT2 receptor, and, especially, are selective agonists of that sub-receptor, for example as may be demonstrated in the tests described below.

15 The compounds of the invention are thus expected to be useful in those conditions in which endogenous production of AngII is deficient and/or where an increase in the effect of AngII is desired or required.

The compounds of the invention are further expected to be useful in those  
20 conditions where AT2 receptors are expressed and their stimulation is desired or required.

The compounds of the invention are further indicated in the treatment of conditions characterised by vasoconstriction, increased cell growth and/or  
25 differentiation, increased cardiac contractility, increased cardiovascular hypertrophy, and/or increased fluid and electrolyte retention.

The compounds of the invention are further indicated in the treatment of stress-related disorders, and/or in the improvement of microcirculation  
30 and/or mucosa-protective mechanisms.

Thus, compounds of the invention are expected to be useful in the treatment of disorders, which may be characterised as indicated above, and which are of, for example, the gastrointestinal tract, the cardiovascular system, the respiratory tract, the kidneys, the eyes, the female reproductive (ovulation) system and the central nervous system (CNS).

Disorders of the gastrointestinal tract that may be mentioned include oesophagitis, Barrett's oesophagus, gastric ulcers, duodenal ulcers, dyspepsia (including non-ulcer dyspepsia), gastro-oesophageal reflux, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), pancreatitis, hepatic disorders (such as hepatitis), gall bladder disease, multiple organ failure (MOF) and sepsis. Other gastrointestinal disorders that may be mentioned include xerostomia, gastritis, gastroparesis, hyperacidity, disorders of the biliary tract, coeliacia, Crohn's disease, ulcerative colitis, diarrhoea, constipation, colic, dysphagia, vomiting, nausea, indigestion and Sjögren's syndrome.

Disorders of the respiratory tract that may be mentioned include inflammatory disorders, such as asthma, obstructive lung diseases (such as chronic obstructive lung disease), pneumonitis, pulmonary hypertension and adult respiratory distress syndrome.

Disorders of the kidneys that may be mentioned include renal failure, nephritis and renal hypertension.

Disorders of the eyes that may be mentioned include diabetic retinopathy, premature retinopathy and retinal microvascularisation.

Disorders of the female reproductive system that may be mentioned include ovulatory dysfunction.

Cardiovascular disorders that may be mentioned include hypertension,  
5 cardiac hypertrophy, cardiac failure, arteriosclerosis, arterial thrombosis,  
venous thrombosis, endothelial dysfunction, endothelial lesions, post-  
balloon dilatation stenosis, angiogenesis, diabetic complications,  
microvascular dysfunction, angina, cardiac arrhythmias, claudicatio  
intermittens, preeclampsia, myocardial infarction, reinfarction, ischaemic  
10 lesions, erectile dysfunction and neointima proliferation.

Disorders of the CNS that may be mentioned include cognitive  
dysfunctions, dysfunctions of food intake (hunger/satiety) and thirst, stroke,  
cerebral bleeding, cerebral embolus and cerebral infarction.

15 Compounds of the invention may also be useful in the modulation of growth  
metabolism and proliferation, for example in the treatment of hypertrophic  
disorders, prostate hyperplasia, autoimmune disorders, psoriasis, obesity,  
neuronal regeneration, the healing of ulcers, inhibition of adipose tissue  
20 hyperplasia, stem cell differentiation and proliferation, cancer (e.g. in the  
gastrointestinal tract, lung cancer, etc), apoptosis, tumours (generally) and  
hypertrophy, diabetes, neuronal lesions and organ rejection.

The compounds of the invention are indicated both in the therapeutic and/or  
25 prophylactic treatment of the above conditions.

According to a further aspect of the present invention, there is provided a  
method of treatment of a condition in which endogenous production of  
AngII is deficient, and/or a condition where an increase in the effect of  
30 AngII is desired or required, and/or a condition where AT2 receptors are

expressed and their stimulation is desired or required, which method comprises administration of a therapeutically effective amount of a compound of the invention to a person suffering from, or susceptible to, such a condition.

5

The compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, by any other parenteral route or *via* inhalation, in a pharmaceutically acceptable dosage form.

10

When the condition to be treated is multiple organ failure, preferred routes of administration are parenteral (e.g. by injection). Otherwise, the preferred route of administration for compounds of the invention is oral.

15

The compounds of the invention may be administered alone, but are preferably administered by way of known pharmaceutical formulations, including tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

20

Such formulations may be prepared in accordance with standard and/or accepted pharmaceutical practice.

25

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including a compound of the invention, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Compounds of the invention may also be administered in combination with other AT2 agonists that are known in the art, as well as in combination with

AT1 receptor antagonists that are known in the art, such as losartan, or in combination with an inhibitor of angiotensin converting enzyme (ACE).

According to a further aspect of the invention, there is provided a  
5 combination product comprising:

(A) a compound of the invention; and

(B) an AT1 receptor antagonist, or an ACE inhibitor,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

10

Such combination products provide for the administration of compound of the invention in conjunction with an AT1 receptor antagonist, or an ACE inhibitor, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises compound of the  
15 invention, and at least one comprises AT1 receptor antagonist, or ACE inhibitor, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including compound of the invention and AT1 receptor antagonist or ACE inhibitor).

20 Thus, there is further provided:

(1) a pharmaceutical formulation including a compound of the invention and an AT1 receptor antagonist, or an ACE inhibitor, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

25

(2) a kit of parts comprising components:

(a) a pharmaceutical formulation including a compound of the invention, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including an AT1 receptor antagonist, or an ACE inhibitor, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier, which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

Depending upon the disorder and patient to be treated and the route of administration, the compounds of the invention may be administered at varying doses.

Although doses will vary from patient to patient, suitable daily doses are in the range of about 1 to 1000 mg per patient, administered in single or multiple doses. More preferred daily doses are in the range 2.5 to 250 mg per patient.

Individual doses of compounds of the invention may be in the range 1 to 100 mg.

In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the condition that is to be treated, as well as the age, weight, sex and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of the invention have the advantage that they bind selectively to, and exhibit agonist activity at, the AT2 receptor. By compounds which "bind selectively" to the AT2 receptor, we include that the affinity ratio for

the relevant compound (AT<sub>2</sub>:AT<sub>1</sub>) is at least 5:1, preferably at least 10:1 and more preferably at least 20:1.

The compounds of the invention may also have the advantage that they may  
5 be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art.

10

### Biological Tests

The following test procedures may be employed.

#### Test A

##### 15 Receptor Binding Assay using Rat Liver Membrane AT<sub>1</sub> Receptor

Rat liver membranes were prepared according to the method of Dudley *et al* (*Mol. Pharmacol.* (1990) 38, 370). Binding of [<sup>125</sup>I]Ang II to membranes was conducted in a final volume of 0.5 mL containing 50 mM Tris-HCl (pH 7.4), 100 mM NaCl, 10 mM MgCl<sub>2</sub>, 1 mM EDTA, 0.025% bacitracin, 0.2%  
20 BSA (bovine serum albumin), liver homogenate corresponding to 5 mg of the original tissue weight, [<sup>125</sup>I]Ang II (70 000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were incubated at 25°C for 1 h, and binding was terminated by filtration through Whatman GF/B glass-fiber filter sheets using a Brandel cell harvester. The filters were washed with 4 ×  
25 2 mL of Tris-HCl (pH 7.4) and transferred to tubes. The radioactivity was measured in a gamma counter. The characteristics of the Ang II binding AT<sub>1</sub> receptor were determined by using six different concentrations (0.03-5 nmol/L) of the labeled [<sup>125</sup>I]AngII. Non-specific binding was determined in the presence of 1 μM Ang II. The specific binding was determined by  
30 subtracting the non-specific binding from the total bound [<sup>125</sup>I]AngII. The



dissociation constant ( $K_d = 1.7 \pm 0.1$  nM,  $[L] = 0.057$  nM) was determined by Scatchard analysis of data obtained with Ang II by using GraFit (Erithacus Software, UK). The binding data were best fitted with a one-site fit. All experiments were performed at least in triplicate.

5

### Test B

#### Receptor Binding Assay using Porcine Myometrial Membrane AT<sub>2</sub> Receptor

Myometrial membranes were prepared from porcine uteri according to the method by Nielsen *et al* (*Clin. Exp. Pharm. Phys.* (1997) **24**, 309). Any possible interference that may be exhibited by binding of compound to AT<sub>1</sub> receptors was blocked by addition of 1  $\mu$ M of a selective AT<sub>1</sub> inhibitor. Binding of [<sup>125</sup>I]Ang II to membranes was conducted in a final volume of 0.5 mL containing 50 mM Tris-HCl (pH 7.4), 100 mM NaCl, 10 mM MgCl<sub>2</sub>, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA, homogenate  
15 corresponding to 10 mg of the original tissue weight, [<sup>125</sup>I]Ang II (70 000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were incubated at 25°C for 1 h, and binding was terminated by filtration through Whatman GF/B glass-fiber filter sheets using a Brandel cell harvester. The  
20 filters were washed with 3  $\times$  3 mL of Tris-HCl (pH 7.4) and transferred to tubes. The radioactivity was measured using a gamma counter. The characteristics of the Ang II binding AT<sub>2</sub> receptor was determined by using six different concentrations (0.03-5 nmol/L) of the labeled [<sup>125</sup>I]Ang II. Non-specific binding was determined in the presence of 1  $\mu$ M Ang II. The  
25 specific binding was determined by subtracting the non-specific binding from the total bound [<sup>125</sup>I]Ang II. The dissociation constant ( $K_d = 0.7 \pm 0.1$  nM,  $[L] = 0.057$  nM) was determined by Scatchard analysis of data obtained with Ang II by using GraFit (Erithacus Software, UK). The binding data were best fitted with a one-site fit. All experiments were performed at least  
30 in triplicate .

Test CDuodenal Mucosal Alkaline Secretion Assay

Compounds were exposed to the duodenal mucosa in barbiturate-  
 5 anaesthetised rats prepared for *in situ* titration of duodenal mucosal alkaline  
 secretion, according to the methodology described by Flemström *et al* in  
*Am. J. Physiol.* (1982) 243, G348.

The invention is illustrated by way of the following examples.

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Example 1*N*-Butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthio-  
 phenene-2-sulfonamide15 (a) *N-tert*-Butylthiophene-2-sulfonamide

Thiophene-2-sulfonyl chloride (15 g, 0.082 mol) was dissolved in CHCl<sub>3</sub>  
 (200 mL) under N<sub>2</sub> atmosphere and then cooled to 0°C. *tert*-Butylamine  
 (25.9 mL, 0.246 mol) dissolved in CHCl<sub>3</sub> (50 mL) was then added dropwise  
 to the reaction mixture. The reaction mixture was stirred for 1 h at room  
 20 temperature and then at reflux for 10 min. Toluene (700 mL) was added  
 and the organic phase was washed with water (3 x 50 mL), dried, and  
 concentrated *in vacuo*. The sub-title product was used without further  
 purification in the next step.

<sup>1</sup>H NMR δ(CDCl<sub>3</sub>): 7.60(1H, dd, J=1.3, 3.8 Hz), 7.53(1H, dd, J=1.3, 5.0  
 25 Hz), 7.02(1H, dd, J=5.0, 3.8 Hz), 5.13(1H, m), 1.24 (9H, m)

<sup>13</sup>C NMR δ(CDCl<sub>3</sub>): 145.0, 131.7, 131.2, 127.0, 55.1, 29.9

(b) 5-*iso*-Butyl-*N-tert*-butylthiophene-2-sulfonamide

*N-tert*-Butylthiophene-2-sulfonamide (10 g, 0.046 mol, see step (a) above)  
 30 was dissolved in THF (85 mL) under N<sub>2</sub> and then cooled to -78°C. *n*-BuLi

(1.6 M, 76.9 mL, 0.12 mol) was added *via* a syringe. The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 30 min. and then at  $-40^{\circ}\text{C}$  for 2 h. Iodo-2-methylpropane (10.5 mL, 0.09 mol) was added dropwise to the reaction mixture. The reaction mixture was stirred overnight at room temperature.

5 The reaction was quenched with  $\text{NH}_4\text{Cl}$  (aq.) and extracted with EtOAc. The combined organic phase was washed with brine and dried and concentrated *in vacuo*. The crude product was purified on column chromatography (hexanes:EtOAc (10:1)) to give the sub-title compound in 55% yield (7.0 g, 0.025 mol).

10  $^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$ : 7.43(1H, d,  $J=3.6$  Hz), 6.67(1H, d,  $J=3.8$  Hz), 4.83(1H, m), 2.67(2H, d,  $J=7$  Hz), 1.88 (1H, m), 1.26(9H, m), 0.93(6H,  $J=6.6$  Hz).  
 $^{13}\text{C}$  NMR  $\delta(\text{CDCl}_3)$ : 145.0, 131.7, 131.2, 127.0, 55.1, 29.9

(c) 5-iso-Butyl-2-(N-tert-butylaminosulfonyl)thiophene-3-boronic acid

15 5-iso-Butyl-N-tert-butylthiophene-2-sulfonamide (10.6 g, 0.039 mol, see step (b) above) was dissolved in THF (165 mL) under  $\text{N}_2$  and then cooled to  $-78^{\circ}\text{C}$ . *n*-BuLi (1.6 M, 60.19 mL, 0.096 mol) was added *via* a syringe. The reaction mixture was stirred at  $-20^{\circ}\text{C}$  for 4 h. The tri-iso-propylborate (13.3 mL, 0.058 mol) was then added *via* a syringe and the reaction mixture was  
 20 stirred overnight at room temperature. The reaction was quenched with 2 M HCl (20 mL). The organic phase was separated and the water phase was extracted with EtOAc (3 x 100 mL). The combined organic phase was washed with brine, dried and concentrated *in vacuo*. The product was used without further purification.

25 MS( $\text{ESI}^+$ )  $m/z$ : 236.8

(d) 1-(4-Bromobenzyl)-1H-imidazole

Dimethyl sulphoxide (20 mL; dried over 4A molecular sieve) was added to potassium hydroxide (2.24 g, 0.04 mol, crushed pellets) and the mixture  
 30 was stirred for 5 min. Imidazole (0.5718 g, 0.0084 mol) was then added

and the mixture was stirred for 2 h. 4-Bromobenzyl bromide (3.25 g, 0.013 mol) was added and the mixture was cooled briefly and stirred for a further 1 h before water (20 mL) was added. The mixture was extracted with ether (3 × 100 mL) and each extract was washed with water (3 × 50 mL). The combined ether layers were dried over CaCl<sub>2</sub> and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel with CHCl<sub>3</sub>:MeOH (30:1) plus 0.05% formic acid as eluent to give the sub-title product (1.275 g, yield: 53%).

<sup>1</sup>H NMR δ(CDCl<sub>3</sub>): 7.73(3H, m), 7.28(3H, m), 7.15(1H, m), 5.30(2H, s)

<sup>13</sup>C NMR δ(CDCl<sub>3</sub>): 136.8, 134.8, 131.5, 129.3, 128.4, 121.5, 118.7, 49.4.

MS(ESI<sup>+</sup>) m/z: 236.8

(e) 3-(4-Imidazol-1-ylmethylphenyl)-5-iso-butyl-N-tert-butylthiophene-2-sulfonamide

5-iso-Butyl-2-(N-tert-butylaminosulfonyl)thiophene-3-boronic acid (200.5 mg, 0.628 mmol, see step (c) above), 1-(4-bromobenzyl)-1H-imidazole (98.8 mg, 0.416 mmol, see step (d) above), toluene (15 mL), ethanol (15 mL), NaOH (1.0M, 1.5 mL, 1.5 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (14.5 mg, 0.125 mmol) were mixed under N<sub>2</sub>. The mixture was warmed to reflux for 2 h. The mixture was diluted with EtOAc (50 mL), washed with water and brine, and dried over MgSO<sub>4</sub>. The solvent was removed and the residue was separated by column chromatography with chloroform:methanol (20:1) as an eluent to give 113.9 mg of the sub-title compound (yield: 63.27%).

IR(neat): 3060, 2996, 1507 cm<sup>-1</sup>

<sup>1</sup>H NMR δ(CDCl<sub>3</sub>): 7.39(1H, s), 7.35(2H, d, J=8.1 Hz), 6.98(2H, d, J=8.1 Hz), 6.96(1H, s), 6.84(H, s), 6.47(H, s), 4.91(2H, s), 3.96(1H, s), 2.72(H, brs), 2.42(2H, d, J=7.1 Hz), 1.64(1H, m), 0.73(9H, s), 0.72(6H, d, J=6.9 Hz)  
<sup>13</sup>C NMR δ(CDCl<sub>3</sub>): 148.6, 142.3, 137.2, 136.2, 135.1, 129.7, 129.4, 128.8, 127.4, 119.2, 54.6, 50.6, 39.2, 30.5, 29.5, 22.1

MS(ESI<sup>+</sup>) m/z: 431.9 Anal. Calcd. for C<sub>22</sub>H<sub>29</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub>: C, 58.8; H, 7.0; N, 9.4. Found: C, 58.7.0; H, 6.7; N, 9.1.

(f) 3-(4-Imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide

5 Trifluoroacetic acid was added (2 mL) to 3-(4-imidazol-1-ylmethylphenyl)-5-iso-butyl-*N-tert*-butylthiophene-2-sulfonamide (113 mg, 0.2618 mmol, see step (e) above) and one drop (*ca.* 0.05 mL) of anisole (*ca.* 0.05 mL) was added to the mixture. The reaction mixture was stirred under N<sub>2</sub> atmosphere for 30 h and then evaporated and co-evaporated with  
10 acetonitrile until TLC showed that it was pure. The crude product was used directly in the next step without further purification.

<sup>1</sup>H NMR δ(CDCl<sub>3</sub>): 7.70(1H,s), 7.57(2H, d, J=8.1 Hz), 7.19(2H, d, J=8.1 Hz), 7.10(1H, s), 6.93(H, s), 6.73(H, s), 5.14(2H, s), 2.67(2H, d, J=7.1 Hz), 2.62(H, brs), 1.94(1H, m), 0.97(6H, d, J=6.6 Hz)

15 <sup>13</sup>C NMR δ(CDCl<sub>3</sub>): 148.4, 142.9, 137.2, 136.2, 134.6, 129.7, 129.3, 128.8, 127.3, 119.2, 50.6, 39.2, 30.5 22.1

MS(EI<sup>+</sup>) m/z: 375.9

(g) *N*-Butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide

20 The crude 3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide from step (f) above was dissolved in pyridine (2 mL, dried over 4Å molecular sieve). Pyrrolidinopyridine (40.52 mg, 0.2618 mmol) and butyl chloroformate (363.5 mg, 0.339 mL) were added to the mixture.  
25 The mixture was stirred overnight under a N<sub>2</sub> atmosphere at room temperature. Evaporation and co-evaporation with acetonitrile to remove the solvents and purification on column chromatography with 10% MeOH in chloroform as eluent gave the title compound (57.8 mg, 0.1217 mmol) in a 46.5% yield (over the last two steps).

30 IR(neat): 3555.8, 3120.3, 2955.9, 1694.2, 1268.5 cm<sup>-1</sup>

$^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$ : 7.96(1H, s), 7.57(2H, d,  $J=7.9$  Hz), 7.10(2H, d,  $J=7.9$  Hz), 6.89(H, s), 6.85(H, s), 6.74(H, s), 5.16(2H, s), 4.03(2H, t,  $J=6.6$  Hz), 2.71(2H, d,  $J=7.1$  Hz), 1.94(1H, m), 1.51(2H, m), 1.25(2H, m), 0.98(6H, d,  $J=6.6$  Hz), 0.87(3H, t,  $J=7.4$  Hz)

5  $^{13}\text{C}$  NMR  $\delta(\text{CDCl}_3)$ : 152.5, 158.4, 143.9, 136.4, 134.6, 133.0, 129.8, 128.9, 127.3, 125.6, 119.6, 65.9, 51.2, 39.3, 30.6, 30.4, 22.3, 18.9, 13.7

MS( $\text{EI}^+$ )  $m/z$ : 476.0 Anal. Calcd for  $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_4\text{S}_2 \cdot \text{H}_2\text{O}$ : C, 56.0; H, 6.3; N, 8.5. Found: C, 56.4; H, 6.2; N, 8.6

## 10 Example 2

### *N*-iso-Butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide

30 mg of crude 3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide (see Example 1(f) above) was dissolved in pyridine (1 mL, dried over 4Å molecular sieve) and cooled on ice. Pyrrolidinopyridine  
15 (11.8 mg, 0.080 mmol) and *iso*-butyl chloroformate (103.6  $\mu\text{L}$ , 0.80 mmol) were then added to the mixture. The mixture was stirred overnight under a  $\text{N}_2$  atmosphere at 50°C. Evaporation and co-evaporation with acetonitrile to remove the solvents, followed by purification by column chromatography  
20 using 10% MeOH in  $\text{CHCl}_3$  as eluent gave the title compound (27 mg, 0.057 mmol) in 71% yield.

$^1\text{H}$  NMR  $\delta(\text{CD}_3\text{OD})$ : 8.18 (brs, 1H), 7.58 (d,  $J = 7.9$  Hz, 2H), 7.32 (d,  $J = 7.9$  Hz, 2H), 7.29 (brs, 1H), 7.17 (brs, 1H), 6.82 (s, 1H), 5.30 (s, 2H), 3.70 (d,  $J = 6.6$  Hz, 2H), 2.72 (d,  $J = 7.1$  Hz, 2H), 1.93 (m, 1H), 1.76 (m, 1H),  
25 0.99 (d,  $J = 6.6$  Hz, 6H), 0.81 (d,  $J = 7.4$  Hz, 6H)

$^{13}\text{C}$  NMR  $\delta(\text{CD}_3\text{OD})$ : 155.7, 150.5, 145.2, 137.0, 136.4, 135.6, 131.0, 130.5, 128.9, 126.6, 121.8, 73.0, 52.2, 40.0, 31.9, 29.1, 22.6, 19.3

MS ( $\text{ESI}^+$ )  $m/z$ : 476.0

Example 3*N*-iso-Propyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide

100 mg of crude 3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide (see Example 1(f) above) was dissolved in pyridine (4 mL, dried over 4Å molecular sieve) and cooled on ice. Pyrrolidinopyridine (39.5 mg, 0.266 mmol) and *iso*-propyl chloroformate (1M in toluene, 2.66 mL, 2.66 mmol) were then added to the mixture. The mixture was stirred overnight under N<sub>2</sub> atmosphere at 50°C. Evaporation and co-evaporation with acetonitrile to remove the solvents, followed by purification using preparative LC/MS (30% acetonitrile to pure acetonitrile, reverse phase) gave the title compound (52.6 mg, 0.114 mmol).

<sup>1</sup>H NMR δ(CD<sub>3</sub>OD): 8.16 (brs, 1H), 7.58 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.32 (s, 1H), 7.18 (s, 1H), 6.84 (s, 1H), 5.32 (s, 2H), 4.72 (sep, *J* = 6.3 Hz, 1H), 2.73 (d, *J* = 7.1 Hz, 2H), 1.94 (m, 1H), 1.09 (d, *J* = 6.3 Hz, 6H), 1.00 (d, *J* = 6.6 Hz, 6H)

<sup>13</sup>C NMR δ(CD<sub>3</sub>OD): 155.5, 151.0, 145.6, 137.2, 136.2, 135.0, 131.0, 130.5, 128.9, 126.8, 122.0, 70.5, 52.1, 40.0, 31.9, 22.6, 22.1

MS (ESI<sup>+</sup>) *m/z*: 462.0

Example 4*N*-(Butoxyacetyl)-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide

CDI (1,1'-carbonyl-diimidazole, 129.5 mg, 0.80 mmol) was added to a solution of butoxyacetic acid (103.8 μL, 0.80 mmol) in dry THF (4 mL). The mixture was stirred at 50°C for 2.5 h. A solution of 3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide (see Example 1(f) above; 100 mg) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 19.9 μL, 0.133 mmol) in dry THF (4 mL) was added to the reaction mixture. The reaction mixture was then stirred overnight at 50°C. MeOH (20 mL) was

added to the reaction mixture, which was then concentrated *in vacuo*. The residue was dissolved in EtOAc (100 mL) and then washed with water (3 x 50 mL). The organic phase was dried and evaporated. The crude product was purified by column chromatography using 10% MeOH in CHCl<sub>3</sub> as eluent to give the title compound (27 mg, 0.057 mmol).

<sup>1</sup>H NMR δ(CD<sub>3</sub>OD): 7.96 (brs, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.21 (brs, 1H), 7.07 (brs, 1H), 6.79 (s, 1H), 5.26 (s, 2H), 3.67 (s, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 2.66 (d, *J* = 6.9 Hz, 2H), 1.88 (m, 1H), 1.48 (m, 2H), 1.29 (m, 4H), 0.96 (d, *J* = 6.6 Hz, 6H), 0.82 (t, *J* = 7.3 Hz, 3H)

<sup>13</sup>C NMR δ(CD<sub>3</sub>OD): 178.3, 148.3, 143.4, 138.0, 137.3, 136.6, 131.1, 130.3, 128.5, 128.2, 127.6, 121.4, 72.4, 72.3, 51.7, 39.9, 32.2, 31.8, 30.7, 22.6, 20.1, 14.3

MS (ESI<sup>+</sup>) *m/z*: 490.1

#### Example 5

##### *N*-Butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-butylthiophene-2-sulfonamide

##### (a) 5-Butylthiophene-2-sulfonic acid *tert*-butylamide

*N-tert*-Butylthiophene-2-sulfonamide (5 g, 0.0228 mol, see Example 1(a) above) was dissolved in THF (43 mL) under N<sub>2</sub> and then cooled to −78°C. *n*-BuLi (1.6 M, 38.5 mL, 0.062 mol) was added *via* a syringe. The reaction mixture was stirred at −78 °C for 30 min and then at −40°C for 2 h. Iodobutane (5.19 mL, 0.046 mol) was added dropwise to the reaction mixture. The reaction mixture was stirred overnight at room temperature, quenched with NH<sub>4</sub>Cl (aq) and extracted with EtOAc. The combined organic phase was washed with brine, dried and concentrated *in vacuo*. The crude product was purified on column chromatography (Hex:EtOAc 10:1) to give the sub-



$^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$ : 7.41 (d,  $J = 3.6$  Hz, 1H), 6.69 (d,  $J = 3.8$  Hz, 1H), 4.96 (m, 1H), 2.80 (d,  $J = 7.6$  Hz, 2H), 1.65 (m, 2H), 1.37 (m, 2H), 1.26 (s, 9H), 0.92 (t,  $J = 7.26$  Hz, 3H)

$^{13}\text{C}$  NMR  $\delta(\text{CDCl}_3)$ : 153.0, 141.7, 131.9, 124.0, 54.9, 33.4, 29.9, 22.0, 13.6.

5

(b) 5-Butyl-2-(*N*-*tert*-butylaminosulfonyl)thiophene-3-boronic acid

5-Butylthiophene-2-sulfonic acid *tert*-butylamide (2.9 g, 0.010 mol, see step (a) above) was dissolved in THF (40 mL) under  $\text{N}_2$  and then cooled to  $-78^\circ\text{C}$ . *n*-BuLi (1.6 M, 16.2 mL, 0.026 mol) was added *via* a syringe. The  
 10 reaction mixture was stirred at  $-20^\circ\text{C}$  for 4 hours. Tri-*iso*-propylborate (13.3 mL, 0.058 mol) was then added *via* a syringe and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with 2 M HCl (20 mL). The organic phase was separated and the water phase was extracted with EtOAc (3 x 100 mL). The combined organic phase was  
 15 washed with brine and dried and concentrated *in vacuo*. The product was used in the next step without further purification.

MS (ESI $^+$ )  $m/z$ : 320.1

(c) 3-(4-Imidazol-1-ylmethylphenyl)-5-butyl-*N*-*tert*-butylthiophene-2-sulfonamide

5-Butyl-2-(*N*-*tert*-butylaminosulfonyl)thiophene-3-boronic acid (300 mg, 1.27 mmol, see step (b) above), 1-(4-bromobenzyl)-1H-imidazole (606 mg, 1.90 mmol, see Example 1(d) above), toluene (15 mL), ethanol (4 mL), NaOH (1.0 M, 4.0 mL, 5.1 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (43.9 mg, 0.038 mmol)  
 25 were mixed under  $\text{N}_2$ . The mixture was warmed to reflux for 2 hours, diluted with EtOAc (50mL), washed with water and brine, and dried over  $\text{MgSO}_4$ . The solvent was removed and the residue was separated by column chromatography using chloroform:methanol (20:1) as eluent. The product was not completely pure but was used in the next step without  
 30 further purification.

(d) 3-(4-Imidazol-1-ylmethylphenyl)-5-butylthiophene-2-sulfonamide

Trifluoroacetic acid was added (10 mL) to the crude 3-(4-imidazol-1-ylmethylphenyl)-5-butyl-*N-tert*-butylthiophene-2-sulfonamide from step (c) above, and one drop (*ca.* 0.05 mL) of anisol was added to the mixture. The reaction mixture was stirred under N<sub>2</sub> atmosphere for 30 hours and then evaporated and co-evaporated with acetonitrile. The crude product was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH (20:1)) to give subtitle compound (232 mg, 0.62 mmol) in 49% yield (from 1-(4-bromobenzyl)-1H-imidazole).

<sup>1</sup>H NMR δ(CDCl<sub>3</sub>, CD<sub>3</sub>OD): 8.97(1H,s), 7.64-7.40 (m, 6H), 6.82 (s, 1H), 5.44 (s, 2H), 2.83 (t, *J* = 7.6 Hz, 2H), 1.68 (m, 1H), 1.39 (m, 1H), 0.95 (t, *J* = 7.26 Hz, 1H)

<sup>13</sup>C NMR δ(CDCl<sub>3</sub>, CD<sub>3</sub>OD): 150.3, 143.8, 136.9, 136.2, 134.9, 131.1, 129.7, 129.3, 123.1, 121.5, 53.3, 34.4, 30.3, 22.9, 14.0

MS (ESI<sup>+</sup>) *m/z*: 376.1

(e) *N*-Butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-butylthiophene-2-sulfonamide

3-(4-Imidazol-1-ylmethylphenyl)-5-butylthiophene-2-sulfonamide (232 mg, 0.62 mmol; see step (d) above) was dissolved in pyridine (3 mL, dried over 4Å molecular sieves). Pyrrolidinopyridine (91.6 mg, 0.618 mmol) and butyl chloroformate (785.7 µL, 0.618 mmol) were added to the mixture. The mixture was stirred overnight under a N<sub>2</sub> atmosphere at room temperature. Evaporation and co-evaporation with acetonitrile to remove the solvents, followed by purification by column chromatography using 10% MeOH in chloroform as eluent, gave the title compound (29 mg, 0.061 mmol) in 10% yield.

<sup>1</sup>H NMR δ(CD<sub>3</sub>OD): 7.94 (s, 1H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.20 (s, 1H), 7.06 (s, 1H), 6.8 (s, 1H), 5.25 (s, 2H), 3.88 (t, *J* = 6.3

Hz, 2H), 2.84 (t,  $J = 7.4$  Hz, 2H), 1.68 (m, 1H), 1.44 (m, 4H), 1.26 (m, 2H), 0.96 (t,  $J = 7.3$  Hz, 3H), 0.87 (t,  $J = 7.3$  Hz, 3H)

$^{13}\text{C}$  NMR  $\delta(\text{CD}_3\text{OD})$ : 159.5, 150.2, 143.9, 138.4, 137.2, 136.6, 131.0, 129.5, 128.5, 128.0, 121.4, 66.5, 51.7, 49.0, 34.7, 32.1, 30.5, 23.2, 20.1,

5 14.1

MS (ESI<sup>+</sup>)  $m/z$ : 476.1

### Example 6

10 *N*-Butyloxycarbonyl-2-(4-imidazol-1-ylmethylphenyl)-4-*iso*-butylbenzene-sulfonamide

#### (a) *N*-*tert*-Butyl-4-*iso*-butylbenzenesulfonamide

Chlorosulfonic acid (28.6 mL, 0.43 mol) was added dropwise to stirred *iso*-butylbenzene (11.14 g, 0.083 mol) at 0°C. The reaction mixture was then  
 15 heated to 40°C for 0.5 h, poured into ice-water (150 mL) and extracted with ethyl acetate (400 mL). The organic phase was washed with water and brine and dried over  $\text{MgSO}_4$ . The solvent was removed *in vacuo* and the residue was dissolved in  $\text{CHCl}_3$  (50 mL). To this stirred solution, *tert*-butylamine (43.7 mL, 0.416 mol) was added dropwise. The reaction was  
 20 heated to reflux for 10 min and then cooled to room temperature. The reaction mixture was then diluted with toluene (200 mL) and washed with water and brine. The organic phase was dried over  $\text{MgSO}_4$  and the solvent was removed *in vacuo*. Purification using column chromatography with hexane:acetone (4:1) as eluent yielded the sub-title compound as a white  
 25 solid (12.0 mg, 0.045 mol) in 54% yield.

IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3266, 2960, 2925, 2871, 1597, 1455

$^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$ : 7.84 (d,  $J = 8.4$  Hz, 2H), 7.27 (d,  $J = 8.3$  Hz, 2H), 5.11 (brs, 1H), 2.55 (d,  $J = 7.3$  Hz, 2H), 1.90 (m, 1H), 1.65 (m, 2H), 1.21 (s, 9H), 0.92 (d,  $J = 6.6$  Hz, 6H)

$^{13}\text{C}$  NMR  $\delta(\text{CDCl}_3)$ : 146.4, 140.7, 129.9, 129.5, 126.8, 54.5, 45.1, 30.1, 22.3

MS (ESI $^+$ )  $m/z$ : 270.0

Anal. Calcd for  $\text{C}_{14}\text{H}_{23}\text{NO}_2\text{S}$ : C, 62.42; H, 8.61; N, 5.20; O, 11.88; S, 11.90;

5 Found: C, 62.2; H, 8.5; N, 5.2

(b) 4-*iso*-Butyl-2-(*N*-*tert*-butylaminosulfonyl)benzene-3-boronic acid

To a solution of *N*-*tert*-butyl-4-*iso*-butyl-benzenesulfonamide (2.69 g, 10 mmol, see step (a)) in THF (50 mL), *n*-BuLi (15.6 mL, 1.6M, 25 mmol) was added dropwise at  $-78^\circ\text{C}$  under an atmosphere of  $\text{N}_2$  (g). The temperature was allowed to rise gradually to  $0^\circ\text{C}$  over 2 h and was then kept at that temperature for 30 min. The reaction mixture was then cooled to  $-40^\circ\text{C}$  and tri-*iso*-propylborate (4.6 mL, 20 mmol) was added. The reaction mixture was stirred overnight at ambient temperature and was quenched with 2M HCl (20 mL). The organic phase was separated and the water phase was extracted with EtOAc (3 x 100 mL). The combined organic phase was washed with brine and dried and concentrated *in vacuo*. The crude product was used in the next step without further purification.

MS (ESI $^+$ )  $m/z$ : 314.0

20

(c) 2-(4-Imidazol-1-ylmethylphenyl)-4-*iso*-butyl-*N*-*tert*-butylbenzene-sulfonamide

The crude product from step (b) above (1.2 g, 3.83 mmol), 1-(4-bromobenzyl)-1H-imidazole (98.8 mg, 0.416 mmol, see Example 1(d) above),  $\text{Pd}(\text{PPh}_3)_4$  (29 mg, 0.25 mmol), NaOH (3 mL, 1M, 3 mmol), toluene (15 mL) and ethanol (3 mL) were mixed under  $\text{N}_2$  (g). The mixture was heated to reflux for 2 h. The reaction mixture was then diluted with ethyl acetate (150 mL) and washed with water and brine. The organic phase was dried over  $\text{MgSO}_4$  and the solvent was removed *in vacuo*. Purification using

25

column chromatography with  $\text{CHCl}_3$ : MeOH (20:1) as eluent yielded the sub-title compound (93.7 mg, 0.220 mmol) in 53% yield.

IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3379, 3293, 3153, 2955, 2868, 1701, 1596, 1505

$^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$ : 8.05 (d,  $J = 8.1$  Hz, 1H), 7.80 (s, 1H), 7.53 (d,  $J = 8.2$  Hz, 2H), 7.30 (m, 3H), 7.07 (m, 3H), 5.24 (s, 2H), 2.56 (d,  $J = 7.1$  Hz, 2H), 1.90 (m, 1H), 1.01 (s, 9H), 0.93 (d,  $J = 6.6$  Hz, 6H)

$^{13}\text{C}$  NMR  $\delta(\text{CDCl}_3)$ : 146.2, 139.9, 138.9, 138.8, 136.7, 135.5, 132.8, 130.3, 128.4, 128.2, 127.9, 126.6, 119.5, 54.0, 50.6, 44.7, 29.8, 29.4, 22.0

MS (ESI<sup>+</sup>)  $m/z$ : 426.1

10

(d) 2-(4-Imidazol-1-ylmethylphenyl)-4-iso-butylbenzene-sulfonamide

To a solution of 2-(4-imidazol-1-ylmethylphenyl)-4-iso-butyl-*N-tert*-butylbenzene-sulfonamide (0.211 mmol, 90.0 mg, see step (c) above) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was added  $\text{BCl}_3$  (1.5 mL, 1M, 1.5 mmol) under  $\text{N}_2$  (g). The mixture was stirred for 0.5 h. Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine and dried over  $\text{MgSO}_4$  and the solvent was removed *in vacuo*. The crude product was used directly in the next step without further purification.

20

(e) *N*-Butyloxycarbonyl-2-(4-imidazol-1-ylmethylphenyl)-4-iso-butylbenzenesulfonamide

The crude product from step (d) above was dissolved in pyridine (2 mL, dried over 4Å molecular sieve). Pyrrolidinopyridine (36 mg, 0.024 mmol) and butyl chloroformate (276  $\mu\text{L}$ , 2.23 mmol) were added to the mixture, which was then stirred for 30 h under  $\text{N}_2$  (g) at room temperature. The solvent was removed *in vacuo* and then co-evaporated with acetonitrile. Purification using column chromatography with  $\text{CHCl}_3$ : MeOH (10:1) as eluent yielded the title compound (66.7 mg, 0.142 mmol) in 68% yield

(from 2-(4-imidazol-1-ylmethylphenyl)-4-*iso*-butyl-*N*-*tert*-butylbenzene-sulfonamide).

IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3129, 3058, 2956, 2869, 1737, 1658, 1466

$^1\text{H}$  NMR  $\delta(\text{CDCl}_3, \text{CH}_3\text{OD})$ : 8.14 (d,  $J = 8.1$  Hz, 1H), 7.72 (s, 1H), 7.36-7.19 (m, 6H), 7.04 (m, 3H), 5.19 (s, 2H), 3.98 (t,  $J = 6.5$  Hz, 2H), 2.56 (d,  $J = 7.1$  Hz, 2H), 1.93 (m, 1H), 1.41 (m, 2H), 1.21 (m, 2H), 0.93 (d,  $J = 6.6$  Hz, 6H), 0.85 (t,  $J = 7.1$  Hz, 3H)

$^{13}\text{C}$  NMR  $\delta(\text{CDCl}_3, \text{CH}_3\text{OD})$ : 151.8, 147.7, 140.4, 139.6, 137.1, 135.3, 134.9, 133.2, 130.5, 129.9, 128.6, 128.0, 127.0, 119.9, 66.3, 45.1, 30.6, 30.1, 22.4, 18.9, 13.6

MS (ESI<sup>+</sup>)  $m/z$ : 470.1

#### Example 7

*N*-Butyloxycarbonyl-5-*iso*-butyl-3-(4-tetrazol-2-ylmethylphenyl)thiophene-2-sulfonamide

(a) 3-(4-Hydroxymethylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide

5-*iso*-Butyl-2-(*N*-*tert*-butylaminosulfonyl)thiophene-3-boronic acid (319.3 mg, 1.00 mmol, see Example 1(c) above), 4-bromobenzyl alcohol (374.1 mg, 2.00 mmol), toluene (20 mL), ethanol (4 mL), NaOH (1.0M, 4 mL, 4 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (34 mg, 0.030mmol) were mixed together under  $\text{N}_2$ . The mixture was warmed to reflux for 2 hours and was then diluted with EtOAc (50 mL), washed with water and brine and dried over  $\text{MgSO}_4$ . The solvent was removed and the residue was separated by column chromatography using  $\text{CHCl}_3$ :MeOH (40:1) as eluent to give 289 mg of the sub-title compound (yield: 76%).

IR(neat): 3465, 3162, 2952, 2867, 1441  $\text{cm}^{-1}$

$^1\text{H}$  NMR  $\delta(\text{CD}_3\text{OD})$ : 7.59(2H, d,  $J = 8.2$  Hz), 7.45(2H, d,  $J = 8.2$  Hz), 6.75(1H, s), 4.75(2H, s), 4.11(1H, brs), 2.69(2H, d,  $J = 7.1$  Hz), 1.92(1H, m), 0.99(6H, d,  $J = 7.2$  Hz), 0.98(9H, s)

$^{13}\text{C}$  NMR  $\delta(\text{CD}_3\text{OD})$ : 148.3, 142.9, 141.1, 134.2, 130.3, 128.9, 127.6,  
5 126.8, 64.8, 54.5, 39.2, 30.5, 29.5, 22.1

MS( $\text{EI}^+$ )  $m/z$ : 382.0

Anal. Calcd for  $\text{C}_{19}\text{H}_{27}\text{NO}_3\text{S}_2$ : C, 59.8; H, 7.3; N, 3.7. Found: C, 59.6; H, 7.0; N, 3.5

10 (b) 3-(4-Bromomethylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide

3-(4-Hydroxymethylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (280 mg, 0.734 mmol, see step (a) above) was dissolved in DMF (10 mL).  $\text{PPh}_3$  (459.2 mg, 1.75 mmol) and  $\text{CBr}_4$  (580.3, 1.75 mmol) were  
15 added to the resultant solution. The mixture was stirred for 24 h at room temperature and then diluted with ethyl acetate. The organic phase was washed with water (50 mL) and brine (50 mL) and then dried over  $\text{MgSO}_4$ . After removing the solvents, the residue was purified by column chromatography using hexane:acetone (5:1) as eluent to give the sub-title  
20 compound (314.9 mg, 0.709 mmol, 76% yield).

IR(neat): 3302, 2952, 2866, 1442  $\text{cm}^{-1}$

$^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$ : 7.62(2H, d,  $J = 8.4$  Hz), 7.48(2H, d,  $J = 8.4$  Hz), 6.75(1H, s), 4.56(2H, s), 4.11(1H, brs), 2.69(2H, d,  $J = 7.1$  Hz), 1.92(1H, m), 0.99(6H, d,  $J = 7.2$  Hz), 0.98(9H, s)

25  $^{13}\text{C}$  NMR  $\delta(\text{CDCl}_3)$ : 148.5, 142.4, 138.2, 136.9, 135.1, 129.5, 129.1, 128.7, 54.6, 39.2, 32.8, 30.5, 29.5, 22.1

MS( $\text{EI}^+$ )  $m/z$ : 445.8

(c) 5-iso-Butyl-N-tert-butyl-3-(4-tetrazol-2-ylmethylphenyl)thiophene-2-sulfonamide

KOH (112.2 mg, 2.00 mmol, crushed pellets) was added to DMSO (10 mL, dried over 4A molecular sieve) and stirred for 5 min. Tetrazole (28.0 mg, 0.4 mmol) was added to the mixture, which was then stirred for 2 h. 3-(4-Bromomethylphenyl)-5-iso-butyl-N-tert-butylthiophene-2-sulfonamide (130 mg, 0.292 mmol, see step (b) above) was added, the mixture was cooled briefly and stirred for an additional hour before water (50 mL) was added. The reaction mixture was extracted with ethyl acetate (250 mL) and the extract was washed with water (2 x 50 mL) and brine (50 mL). The organic phase was dried over MgSO<sub>4</sub> and the solvent was removed *in vacuo*. The residue was purified on column chromatography using hexane:acetone (3:1) as eluent to give the sub-title compound (28.6 mg, 0.066 mmol, 23% yield). IR(neat): 3328, 3134, 2980, 1501, 1466 cm<sup>-1</sup>. <sup>1</sup>H NMR δ(CDCl<sub>3</sub>): 8.52(1H, s), 7.64(2H, d, J= 8.3 Hz), 7.46(2H, d, J= 8.3 Hz), 6.73(1H, s), 5.85(2H, s), 2.69(2H, d, J= 7.1 Hz), 1.91(1H, m), 1.58(1H, s), 0.98(15H, brs). <sup>13</sup>C NMR δ( CDCl<sub>3</sub>): 153.2, 148.5, 142.4, 136.8, 135.8, 133.2, 129.7, 128.8, 128.5, 56.3, 54.6, 39.2, 30.5, 29.5, 22.1. MS(EI<sup>+</sup>) m/z: 434.0. Anal. Calcd for C<sub>20</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub> × H<sub>2</sub>O: C, 53.2; H, 6.5; N, 15.5. Found: C, 53.7; H, 6.1; N, 15.2

(d) 5-iso-Butyl-3-(4-tetrazol-2-ylmethylphenyl)thiophene-2-sulfonamide

To a solution of 5-iso-butyl-N-tert-butyl-3-(4-tetrazol-2-ylmethylphenyl)-thiophene-2-sulfonamide (42.1 mg, 0.111 mmol, see step (c) above) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added BCl<sub>3</sub> (0.5 mL, 1M, 0.5 mmol) under N<sub>2</sub> (g). The reaction mixture was stirred for 0.5 h. Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine and dried over MgSO<sub>4</sub> and the



solvent was removed *in vacuo*. The crude product was used directly in the next step without further purification.

(e) *N*-Butyloxycarbonyl-5-*iso*-butyl-3-(4-tetrazol-2-ylmethylphenyl)thiophene-2-sulfonamide

The crude product from step (d) above was dissolved in pyridine (1 mL, dried over 4Å molecular sieve). Pyrrolidinopyridine (14 mg, 0.0095 mmol) and butyl chloroformate (120 µL, 0.97 mmol) were added to the mixture, which was then stirred for 30 hours under N<sub>2</sub>(g) at room temperature. The solvent was removed *in vacuo* and then co-evaporated with acetonitrile. Purification using column chromatography with CHCl<sub>3</sub>:MeOH (35:1) as eluent yielded the title compound (24.9 mg, 0.052 mmol) in 54% yield (from 5-*iso*-butyl-*N*-*tert*-butyl-3-(4-tetrazol-2-ylmethylphenyl)thiophene-2-sulfonamide).

IR(neat): 3330, 2961, 2875, 1743, 1466 cm<sup>-1</sup>

<sup>1</sup>H NMR δ(CDCl<sub>3</sub>): 8.49(1H, s), 7.68(1H, s), 7.48(2H, d, J= 8.2 Hz), 7.40(2H, d, J=8.2 Hz), 6.73(1H, s), 5.82(2H, s), 4.07(2H, t, J= 6.6 Hz), 2.70(2H, d, J= 7.1 Hz), 1.91(1H, m), 1.50(2H, m), 1.24(2H, m), 0.98(6H, d, J= 6.9 Hz), 0.87(3H, J= 7.4 Hz)

<sup>13</sup>C NMR δ( CDCl<sub>3</sub>): 153.2, 151.8, 150.1, 145.6, 134.8, 133.4, 129.6, 129.3, 128.3, 66.9, 56.3, 39.2, 30.5, 30.4, 22.2, 18.7, 13.6

MS(EI<sup>+</sup>) m/z: 478.0

Anal. Calcd for C<sub>21</sub>H<sub>27</sub>N<sub>5</sub>O<sub>4</sub>S<sub>2</sub>: C, 52.8; H, 5.7; N, 14.7. Found: C, 53.0; H, 5.8; N, 14.1

Example 8*N*-Butyloxycarbonyl-5-*iso*-butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide5 (a) 1-(4-Bromobenzyl)-1*H*-tetrazole

Dimethyl sulphoxide (10 mL, dried over 4A molecular sieve) was added to potassium hydroxide (1.12 g, 0.02 mol, crushed pellets) and the mixture was stirred for 5 minutes. 1*H*-Tetrazole (0.35 g, 0.005 mol) was then added and the mixture was stirred for 2 hours. 4-Bromobenzyl bromide (1.87 g, 10 0.0075 mol) was added and the mixture was cooled briefly and stirred for a further hour before adding water (50 mL). The mixture was extracted with ether (3 × 80 mL) and each extract was washed with water (3 × 50 mL). The combined ether layers were dried over MgSO<sub>4</sub> and the solvent using removed *in vacuo*. The residue was chromatographed on silica gel with 15 CHCl<sub>3</sub>:MeOH (40:1) as eluent yielding the sub-title compound (0.98 g, yield: 82%).

<sup>1</sup>H NMR δ(CDCl<sub>3</sub>): 8.64(1H, s), 7.50(2H, d, J= 8.4 Hz), 7.18(2H, d, J= 8.4), 5.56(2H, s)

<sup>13</sup>C NMR δ(CDCl<sub>3</sub>): 142.4, 132.4, 131.8, 129.9, 123.4, 51.3

20 MS(ESI<sup>+</sup>) m/z: 238.8

Anal. Calcd. for C<sub>8</sub>H<sub>7</sub>BrN<sub>4</sub>: C, 40.2; H, 3.0; N, 23.4. Found: C, 40.3; H, 3.0; N, 23.4

25 (b) 5-*iso*-Butyl-*N*-*tert*-butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide

5-*iso*-Butyl-2-(*N*-*tert*-butylaminosulfonyl)thiophene-3-boronic acid (401.0 mg, 1.256 mmol, see Example 1(c) above), 1-(4-bromobenzyl)-1*H*-tetrazole (199.4 mg, 0.834 mmol, see step (a) above), toluene (20 mL), ethanol (3.0 mL), NaOH (1.0M, 5.0 mL, 5.0 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (29.0 mg, 0.25 mmol) 30 were mixed under N<sub>2</sub>. The mixture was warmed to reflux for 2 hours. The

mixture was diluted with EtOAc (20 mL), washed with water and brine, and dried over MgSO<sub>4</sub>. The solvent was removed and the residue was separated by column chromatography using CHCl<sub>3</sub>:MeOH (40:1) as eluent to give 222.4 mg of the sub-title compound (yield: 62%).

5 IR(neat): 3284, 3134, 2958, 2870, 1513, 1436 cm<sup>-1</sup>

<sup>1</sup>H NMR δ(CDCl<sub>3</sub>): 8.71(1H, s), 7.64(2H, d, J= 8.3 Hz), 7.40(2H, d, J= 8.3 Hz), 6.74(1H, s), 5.65(2H, s), 2.67(2H, d, J= 7.1 Hz), 1.94(1H, m), 0.99(15H, m)

<sup>13</sup>C NMR δ(CDCl<sub>3</sub>): 148.5, 142.6, 142.2, 136.8, 135.9, 133.1, 129.9, 128.8,  
10 128.3, 54.6, 51.7, 39.2, 30.5, 29.5, 22.1

MS(ESI<sup>+</sup>) m/z: 433

(c) 5-iso-Butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide

BCl<sub>3</sub> (1.0 mL, 1M, 1.0 mmol) was added to a solution of 5-iso-butyl-*N-tert*-  
15 butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide (177.0 mg, 0.408 mmol, see step (b) above) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) under N<sub>2</sub> (g), and the reaction mixture was stirred for 0.5 h. Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine, dried over MgSO<sub>4</sub> and the solvent  
20 was removed *in vacuo*. The crude product was used directly in the next step used without further purification.

(d) *N*-Butyloxycarbonyl-5-iso-butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide

25 The title compound was prepared (89.6 mg, 0.188 mmol, 46% yield (from 5-iso-butyl-*N-tert*-butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide)) analogously to the procedure described in Example 7(e) above from the crude 5-iso-butyl-3-(4-tetrazol-1-ylmethylphenyl)-thiophene-2-sulfonamide from step (c) above.

30 IR(neat): 3135, 2959, 2875, 1747, 1464 cm<sup>-1</sup>

$^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$ : 8.73(1H, s), 7.43(2H, d,  $J=7.7$  Hz), 7.24(2H, d,  $J=7.7$  Hz), 6.72(1H, s), 5.59(2H, s), 4.00(2H, brs), 2.69(2H, brs), 1.91(1H, m), 1.46(2H, m), 1.19(2H, m), 0.95(6H, d,  $J=6.9$  Hz), 0.83(3H,  $J=6.8$  Hz)

$^{13}\text{C}$  NMR  $\delta(\text{CDCl}_3)$ : 151.8, 151.4, 145.3, 143.0, 134.8, 133.5, 129.6, 129.1,  
 5 127.8, 66.9, 51.4, 39.2, 30.9, 30.4, 22.2, 18.7, 13.6

MS( $\text{EI}^+$ )  $m/z$ : 478.0

Anal. Calcd for  $\text{C}_{21}\text{H}_{27}\text{N}_5\text{O}_4\text{S}_2 \times \frac{1}{2} \text{H}_2\text{O}$ : C, 51.8; H, 5.8; N, 14.4. Found: C, 51.4; H, 5.6; N, 14.1

#### 10 Example 9

*N*-Butyloxycarbonyl-3-(4-[1,2,4]triazol-1-ylmethylphenyl)-5-*iso*-butyl-thiophene-2-sulfonamide

(a) 1-(4-Bromobenzyl)-1*H*-[1,2,4]triazole

15 DMF and KOH (3.3 g, 58 mmol) were stirred together at rt for 5 minutes before adding 1,2,4-triazole (1 g, 14.5 mmol). After a further 30 minutes, the reaction mixture was cooled to 0°C and 1-bromo-4-bromomethylbenzene (7.2 g, 29 mmol) was added dropwise over 5 minutes. The reaction mixture was heated to 60°C, then cooled to rt, extracted with ethyl acetate  
 20 and water, and subsequently dried over  $\text{K}_2\text{CO}_3$ . The solvent was evaporated to yield yellow-white crystals, which, upon repeated recrystallisation, (ethylacetate/isohexane) yielded 0.60 g of the sub-title compound as white crystals (62% isolated yield).

$^1\text{H}$  NMR  $\delta(270 \text{ MHz}, \text{CDCl}_3)$ : 8.11 (s, 1H), 7.96 (s, 1H), 7.51-7.38 (m, 2H),  
 25 7.15-7.10 (m, 2H), 5.29 (s, 2H)

$^{13}\text{C}$  NMR  $\delta(67.8 \text{ MHz}, \text{CDCl}_3)$ : 152.2, 143.0, 133.5, 132.1, 129.5, 122.7, 52.8

MS  $m/z$  238 ( $\text{M}^+ + 1$ )

(b) 3-(4-[1,2,4]Triazol-1-ylmethylphenyl)-5-iso-butyl-N-tert-butylthiophene-2-sulfonamide

5-iso-Butyl-2-(N-tert-butylaminosulfonyl)thiophene-3-boronic acid (0.479 g, 1.5 mmol, see Example 1(c) above), 1-(4-bromobenzyl)-1H-[1,2,4]triazole (0.238 g, 1 mmol, see step (a) above), Pd(OAc)<sub>2</sub> (15.7 mg, 0.03 mmol), triphenyl phosphine (15.7 mg, 0.06 mmol) and NaOH (0.16 g, 4 mmol) were dissolved in 4 mL of toluene/ethanol (4:1) in a thick walled glass tube, and were then heated to 80°C for 1 h. The reaction mixture was cooled to rt, extracted with ethyl acetate and water and subsequently dried over K<sub>2</sub>CO<sub>3</sub>. The solvent was evaporated and the reaction mixture was separated on a silica column (dichloromethane + 1% methanol to dichloromethane + 4% methanol) to yield 0.288 g of the sub-title compound (65% yield).

<sup>1</sup>H NMR δ(270 MHz, CDCl<sub>3</sub>): 8.13 (s, 1H), 7.94 (s, 1H), 7.60-7.57 (m, 2H), 7.33-7.30 (m, 2H), 6.72 (s, 1H), 5.37 (s, 2H), 4.47 (s, 1H), 2.65, (d, *J* = 7 Hz, 2H), 1.89 (sept *J* = 7 Hz, 1H), 0.96 (s, 9H), 0.94 (d, *J* = 7 Hz, 6H)

<sup>13</sup>C NMR δ(67.8 MHz, CDCl<sub>3</sub>): 152.1, 148.5, 143.1, 142.3, 136.6, 135.2, 134.8, 129.6, 128.8, 128.0, 54.5, 53.1, 39.1, 30.4, 29.4, 22.1

MS *m/z* 433 (*M*<sup>+</sup> + 1)

(c) 3-(4-[1,2,4]Triazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide

3-(4-[1,2,4]Triazol-1-ylmethylphenyl)-5-iso-butyl-N-tert-butylthiophene-2-sulfonamide (146.4 mg, 0.34 mmol, see step (b) above) was mixed with BCl<sub>3</sub> (1M solution in hexane) (2 mL, 1.7 mmol) in 5 mL of dichloromethane at rt and stirred for 1 h. The reaction mixture was extracted with ethyl acetate and water and subsequently dried over K<sub>2</sub>CO<sub>3</sub>. The solvent was evaporated and the resultant product was sufficiently pure to be used directly in the next step.

(d) N-Butyloxycarbonyl-3-(4-[1,2,4]triazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide

59 mg (0.16 mmol) of the crude 3-(4-[1,2,4]triazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide from step (c) above was mixed with butyl chloroformate (31  $\mu$ L, 0.24 mmol) and 4-dimethylaminopyridine (2 mg, 16  $\mu$ mol) in 5 mL of triethylamine at 0°C. The reaction mixture was stirred overnight and then diluted with ethyl acetate, washed with water and dried over K<sub>2</sub>CO<sub>3</sub>. The reaction mixture was then separated on a silica column (dichloromethane + 15% methanol), circular chromatography (dichloromethane + 10-15% methanol and preparative LC-MS to yield 7.0 mg of the title compound (9% isolated yield).

<sup>1</sup>H NMR  $\delta$ (270 MHz, CDCl<sub>3</sub>): 8.11 (s, 1H), 7.98 (s, 1H), 7.50-7.47 (m, 2H), 7.29-7.26 (m, 2H), 6.74 (s, 1H), 5.39 (s, 2H), 4.05 (t, *J* = 7 Hz, 2H), 2.71 (d, *J* = 7 Hz, 2H), 1.95 (sept, *J* = 7 Hz, 1H), 1.52 (pent, *J* = 7 Hz, 2H), 1.26 (sext, *J* = 7 Hz, 2H), 0.99 (d, *J* = 7 Hz, 6H), 0.88 (t, *J* = 7 Hz, 3H)

<sup>13</sup>C NMR  $\delta$ (67.8 MHz, CDCl<sub>3</sub>): 151.9, 151.1, 145.1, 143.4, 134.7, 134.2, 131.6, 129.7, 129.0, 127.8, 66.3, 53.2, 39.2, 30.4, 30.3, 22.1, 18.7, 13.5

MS *m/z* (relative intensity 30 eV) 477 (*M*<sup>+</sup> + 1)

20 Example 10

N-(Butylamino)carbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide

(a) 1-(4-Bromobenzyl)-1H-imidazole

25 Dimethyl sulphoxide (20 mL, dried over 4Å molecular sieves) was added to potassium hydroxide (2.24 g, 0.04 mol, crushed pellets) and the mixture was stirred for 5 min. Imidazole (0.5718 g, 0.0084 mol) was then added and the mixture was stirred for 2 hours. 4-Bromobenzyl bromide (3.25 g, 0.013 mol) was added and the mixture was cooled briefly and stirred for a further hour before adding water (20 mL). The mixture was extracted with

ether (3 × 100 mL) and each extract was washed with water (3 × 50 mL). The combined ether layers were dried over CaCl<sub>2</sub> and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel with CHCl<sub>3</sub>/MeOH (30:1) plus 0.05% formic acid as eluent yielding the sub-title compound (1.275 g, yield: 53%).

<sup>1</sup>H NMR δ(CDCl<sub>3</sub>): 7.73 (m, 3H), 7.28 (m, 3H), 7.15 (m, 1H), 5.30 (s, 2H)

<sup>13</sup>C NMR δ(CDCl<sub>3</sub>): 136.8, 134.8, 131.5, 129.3, 128.4, 121.5, 118.7, 49.4

MS (ESI<sup>+</sup>) *m/z*: 236.8

10 (b) 3-(4-Imidazol-1-ylmethylphenyl)-5-iso-butyl-N-tert-butylthiophene-2-sulfonamide

5-iso-Butyl-2-(*N*-tert-butylaminosulfonyl)thiophene-3-boronic acid (200.5 mg, 0.628 mmol, see Example 1(c) above), 1-(4-bromobenzyl)-1H-imidazole (98.8 mg, 0.416 mmol, see step (a) above), toluene (15 mL),  
15 ethanol (15 mL), NaOH (1.0M, 1.5 mL, 1.5 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (14.5 mg, 0.125 mmol) were mixed under N<sub>2</sub>. The mixture was warmed to reflux for 2 hours. The mixture was diluted with EtOAc (50 mL), washed with water and brine, and dried over MgSO<sub>4</sub>. The solvent was removed and the residue was separated by column chromatography with chloroform:methanol (20:1)  
20 as eluent to give 113.9 mg of the sub-title compound (yield: 63.27%).

IR (neat, cm<sup>-1</sup>) ν 3060, 2996, 1507

<sup>1</sup>H NMR δ(CDCl<sub>3</sub>): 7.39 (s, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.1 Hz, 2H), 6.96 (s, 1H), 6.84 (s, 1H), 6.47 (s, 1H), 4.91 (s, 2H), 3.96 (s, 1H), 2.72 (brs, 1H), 2.42 (d, *J* = 7.1 Hz, 2H), 1.64 (m, 1H), 0.73 (s, 9H), 0.72 (d, *J* = 6.9 Hz, 6H)

<sup>13</sup>C NMR δ(CDCl<sub>3</sub>): 148.6, 142.3, 137.2, 136.2, 135.1, 129.7, 129.4, 128.8, 127.4, 119.2, 54.6, 50.6, 39.2, 30.5, 29.5, 22.1

MS (ESI<sup>+</sup>) *m/z*: 431.9

Anal. Calcd for C<sub>22</sub>H<sub>29</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub>: C, 58.8; H, 7.0; N, 9.4. Found: C, 58.70; H, 6.7; N, 9.1

(c) 3-(4-Imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide

To a solution of 3-(4-imidazol-1-ylmethylphenyl)-5-iso-butyl-N-*tert*-butylthiophene-2-sulfonamide (0.097 mmol, 42.0 mg, see step (b) above) in  
 5 CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added BCl<sub>3</sub> (0.5 mL, 1M, 0.5 mmol) under N<sub>2</sub> (g). The mixture was stirred for 0.5 h. Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine and dried over MgSO<sub>4</sub> and the solvent was removed *in vacuo*. The crude product was used directly in the  
 10 next step without further purification.

(d) N-(Butylamino)carbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide

The crude product from step (c) above was dissolved in acetone (5 mL)  
 15 under N<sub>2</sub> (g). NaOH (0.20 mL, 1M, 0.20 mmol) was added to the mixture, which was then stirred for 10 min. Butyl isocyanate (109  $\mu$ L, 0.97 mmol) was then added and the mixture was stirred overnight at room temperature. The reaction mixture was then diluted with ethyl acetate (150 mL) and washed with water and brine. The organic phase was dried over MgSO<sub>4</sub>  
 20 and the solvent was removed *in vacuo*. Purification using column chromatography with CHCl<sub>3</sub>:MeOH (10:1) as eluent yielded the title compound (15.1 mg, 0.032 mmol) in 33% yield (from 3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonic acid *tert*-butylamide).

IR (neat, cm<sup>-1</sup>)  $\nu$  3261, 3120, 2957, 2869, 1701, 1514

25 <sup>1</sup>H NMR  $\delta$ (CDCl<sub>3</sub>, CH<sub>3</sub>OD): 7.64 (s, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.97 (brs 1H), 6.90 (brs, 1), 6.72 (s, 1H), 6.24 (brs, 1H), 5.10 (s, 2H), 3.08 (m, 2H), 2.62 (d, *J* = 7.1 Hz, 2H), 1.92 (m, 1H), 1.20 (m, 4H), 0.99 (d, *J* = 6.6, 6H), 0.86 (t, *J* = 7.1 Hz, 3H)



$^{13}\text{C}$  NMR  $\delta(\text{CDCl}_3, \text{CH}_3\text{OD})$ : 152.2, 150.0, 144.5, 137.0, 135.9, 134.4, 133.0, 129.7, 129.5, 128.1, 127.1, 119.5, 50.7, 39.9, 39.2, 31.6, 30.5, 22.2, 19.8, 13.7

MS ( $\text{ESI}^+$ )  $m/z$ : 475.2

5

### Example 11

#### *N*-Butylsulfonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide

Crude 3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide (prepared according to the procedure described in Example 10(c) above) was dissolved in THF (3 mL) under  $\text{N}_2$  (g). NaOH (1.0 mL, 1M, 1.0 mmol) was added to the mixture, which was then stirred for 10 min. Butanesulfonyl chloride (45  $\mu\text{L}$ , 0.35 mmol) was then added, and the mixture was stirred for 24 h at room temperature. The reaction mixture was then diluted with ethyl acetate (150 mL) and washed with water and brine. The organic phase was dried over  $\text{MgSO}_4$  and the solvent was removed *in vacuo*. The crude product was recrystallised from acetone to yield the title compound (31.7 mg, 0.064 mmol).

IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3133, 2959, 2871, 1576, 1543, 1514

$^1\text{H}$  NMR  $\delta(\text{CDCl}_3, \text{CH}_3\text{OD})$ : 8.70 (s, 1H), 7.64 (d,  $J = 8.1$  Hz, 2H), 7.08-7.20 (m, 5H), 6.59 (s, 1H), 5.06 (s, 2H), 3.08 (m, 2H), 2.57 (d,  $J = 7.1$  Hz, 2H), 1.67 (m, 1H), 1.65 (m, 2H), 1.29 (m, 2H), 0.89-0.79 (m, 9H)

$^{13}\text{C}$  NMR  $\delta(\text{CDCl}_3, \text{CH}_3\text{OD})$ : 146.8, 140.9, 138.2, 136.8, 135.0, 131.9, 130.4, 128.6, 127.9, 121.2, 119.8, 54.0, 52.5, 38.9, 30.3, 25.6, 21.9, 21.4, 13.4

MS ( $\text{ESI}^+$ )  $m/z$ : 496.1

Example 12*N*-Butylsulfonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-carboxamide5 (a) 2-*iso*-Butylthiophene

A solution of thiophene (6.00 g, 0.0714 mol) in 80 mL of THF (80 mL) was treated with *n*-BuLi (1.6 M in hexane, 54 mL, 0.0864 mol) at -78°C. The mixture was stirred at -40°C for about 2 hours. The solution was then cooled to -78°C again and treated with 2-methylpropyliodide (16.04 g, 0.0871 mol). The solution was stirred at 0°C for 2 hours, and then overnight at room temperature for about 16 hours. The solution was treated with water (25 mL) and extracted with petroleum ether (3 x 25 mL). The organic layer was dried over magnesium sulfate and filtered. The crude product was purified by distillation (54-55°C at 12 mmHg) to give the sub-  
 10 title compound (3.0 g, 0.0213 mol) in 30% yield.

<sup>1</sup>H NMR δ(CDCl<sub>3</sub>): 7.14 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.95 (dd, *J* = 5.1, 3.3 Hz, 1H), 6.79 (dd, *J* = 3.3, 1.2 Hz, 1H), 2.72 (d, *J* = 7.1 Hz, 2H), 1.92 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 3H)

<sup>13</sup>C NMR δ(CDCl<sub>3</sub>): 144.3, 126.5, 124.8, 123.0, 39.1, 30.8, 22.2

20 MS(EI<sup>+</sup>) *m/z*: 140

(b) 5-*iso*-Butyl-*N*-*tert*-butylthiophene-2-carboxamide

To 2-*iso*-butylthiophene (1 g, 7.143 mmol, see step (a) above) in THF (15mL) was added *n*-BuLi (1.6 M in hexane, 5.3 mL, 8.48 mmol) at -78°C and the reaction mixture was stirred at 0°C for 2 hours. *tert*-Butyl-  
 25 isocyanate (897 μL, 7.86 mmol) was then added to the mixture at -78°C. The stirred solution was kept at 0°C for an additional 2 hours. The reaction mixture was then quenched with H<sub>2</sub>O (15 mL) and extracted with EtOAc (3 x 20 mL). The organic layer was dried over MgSO<sub>4</sub>, concentrated and  
 30 purified using silica gel column chromatography (10:90 petroleum ether-

EtOAc) to give the sub-title compound (1.2 g, 5.01 mmol) as white needles in 70% yield.

$^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$ : 7.24 (d,  $J = 3.6$  Hz, 1H), 6.69 (d,  $J = 3.6$  Hz, 1H), 5.72 (brs, 1H), 2.65 (d,  $J = 7.2$  Hz, 2H), 1.88 (m, 1H), 1.44 (s, 9H), 0.93 (d,  $J =$   
5 6.6 Hz, 3H)

$^{13}\text{C}$  NMR  $\delta(\text{CDCl}_3)$ : 161.4, 149.2, 137.6, 127.5, 125.5, 51.8, 39.5, 30.7, 28.9, 22.1

IR(neat): 3215, 2924, 1620, 1550, 1464,  $\text{cm}^{-1}$

Anal. Calcd. for  $\text{C}_{13}\text{H}_{21}\text{NOS}$ : C, 65.2; H, 8.8; N, 5.9. Found: C, 65.5; H, 8.9;  
10 N, 5.9.

MS( $\text{EI}^+$ )  $m/z$ : 239

(c) 5-iso-Butyl-*N*-tert-butylthiophene-2-carboxamide-3-boronic acid

To a solution of 5-iso-butyl-*N*-tert-butylthiophene-2-carboxamide (from  
15 step (b) above; 0.5 g, 2.1 mmol) in THF (50 mL) was added 3.3 mL *n*-BuLi (1.6M in hexane, 3.3 mL, 5.28 mmol) at  $-78^\circ\text{C}$ . The reaction mixture was slowly warmed to  $-20^\circ\text{C}$  and stirred for 4 hours. Tri-*iso*-propylborate (0.59 g, 3.14 mmol) was added to the mixture at  $-78^\circ\text{C}$ . The solution was slowly warmed to room temperature and stirred overnight. The reaction was  
20 quenched with HCl(aq) (2M, 2 mL) and extracted with EtOAc (2 x 25 mL), washed with brine, dried with  $\text{MgSO}_4$  and concentrated. The crude product was used in the next step without further purification.

MS( $\text{EI}^+$ )  $m/z$ : 284

(d) 3-(4-Imidazol-1-ylmethylphenyl)-5-iso-butyl-*N*-tert-butylthiophene-2-carboxamide

5-iso-Butyl-*N*-tert-butylthiophene-2-carboxamide-3-boronic acid (200 mg, 0.706 mmol, see step (c) above), 1-(4-bromobenzyl)-1H-imidazole (80 mg, 0.337 mmol), toluene (5 mL), ethanol (2 mL), NaOH (1.63 M, 0.84 mL,  
30 1.38 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (16.3 mg, 0.014 mmol) were mixed together

under N<sub>2</sub>. The resultant mixture was warmed to reflux for 2 hours. The mixture was diluted with EtOAc (50 mL), washed with water and brine, and dried over MgSO<sub>4</sub>. The solvent was removed and the residue was separated by column chromatography with chloroform:methanol (95:5) as eluent to give 99 mg of the sub-title compound (yield: 74%).

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>): 7.55 (br s, 1H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.09 (br s, 1H), 6.89 (br s, 1H), 6.63 (s, 1H), 5.25 (br s, 1H), 5.16 (s, 2H), 2.63 (d, *J* = 6.9 Hz, 2H), 1.89 (m, 1H), 1.13 (s, 9H), 0.95 (d, *J* = 6.6 Hz, 3H)

<sup>13</sup>C NMR δ(CDCl<sub>3</sub>): 161.4, 147.4, 140.2, 137.3, 136.3, 136.1, 133.9, 130.0, 129.8, 128.3, 127.6, 119.0, 51.4, 50.4, 39.3, 30.5, 28.4, 22.2

IR(neat): 3113 2930, 1645, 1512 cm<sup>-1</sup>

MS(EI<sup>+</sup>) *m/z*: 396

Anal. Calcd. for C<sub>23</sub>H<sub>29</sub>N<sub>3</sub>OS + H<sub>2</sub>O: C, 66.8; H, 7.6; N, 10.2. Found: C, 67.0; H, 7.6; N, 9.9.

(e) 3-(4-Imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-carboxamide

Trifluoroacetic acid was added (2.5 mL) to 3-(4-imidazol-1-ylmethylphenyl)-5-iso-butyl-*N-tert*-butylthiophene-2-carboxamide (165 mg, 0.417 mmol, see step (d) above), and one drop (*ca.* 0.05 mL) of anisol was added to the reaction mixture. The mixture was stirred under a N<sub>2</sub> atmosphere for 30 hours and then evaporated and co-evaporated with acetonitrile. The crude product was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH (85:15)) to give the sub-title compound (117 mg, 0.345 mmol) in 73% yield.

<sup>1</sup>H NMR δ(CD<sub>3</sub>OD): 9.05 (br s, 1H), 7.63 (br s, 1H), 7.55 (br s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 6.81 (s, 1H), 5.47 (s, 2H), 2.68 (d, *J* = 7.1 Hz, 2H), 1.90 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H)

<sup>13</sup>C NMR δ(CD<sub>3</sub>OD): 167.1, 148.9, 144.1, 137.9, 136.6, 135.1, 131.2, 130.8, 130.1, 129.8, 123.3, 121.6, 53.4, 40.0, 31.8, 22.5

IR(neat): 3308, 2957, 1657, 1509, 1461

MS(EI<sup>+</sup>) m/z: 340

Anal. Calcd. for C<sub>19</sub>H<sub>21</sub>N<sub>3</sub>OS: C, 67.2; H, 6.2; N, 12.4. Found: C, 67.5; H, 6.4; N, 12.3.

5

(f) *N*-Butylsulfonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-carboxamide

NaH (55%, 12 mg, 0.28 mmol) was added to a solution of 3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-carboxamide (46 mg, 0.136 mmol, see step (e) above) in THF (1 mL). The mixture was stirred at 50°C for 0.5 hours. Butanesulfonyl chloride (29  $\mu$ L, 0.223 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 1 hour. The mixture was concentrated and purified using silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH, 9:1) to give 31 mg of the title compound as a white powder (yield: 50%).

<sup>1</sup>H NMR  $\delta$ (CDCl<sub>3</sub>): 7.82 (br s, 1H), 7.32 (br s, 2H), 7.06 (d, *J* = 7.4 Hz, 2H), 6.95 (br s, 2H), 6.64 (s, 1H), 5.09 (br s, 2H), 4.79 (br s, 1H), 2.97 (br s, 2H), 2.62 (d, *J* = 6.9 Hz, 2H), 1.90 (m, 1H), 1.65 (br s, 2H), 1.29 (m, 2H), 0.95 (d, *J* = 6.5 Hz, 6H), 0.81 (t, *J* = 6.6 Hz, 3H)

<sup>13</sup>C NMR  $\delta$ (CDCl<sub>3</sub>): 166.4, 148.9, 144.3, 137.3, 136.4, 134.8, 132.2, 130.0, 129.4, 127.2, 119.9, 53.2, 51.0, 39.5, 30.5, 25.4, 22.3, 21.5, 13.6

MS(EI<sup>+</sup>) m/z: 460

Anal. Calcd. for C<sub>23</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>S<sub>2</sub> + H<sub>2</sub>O: C, 57.8; H, 6.5; N, 8.8. Found: C, 58.1; H, 6.4; N, 8.3.

IR(neat): 3482, 3118, 2958, 1558, 1456 cm<sup>-1</sup>

Example 13

The following compounds were also prepared in accordance with techniques described herein:

(i) *N*-butyloxycarbonyl-4-butyl-2-(4-imidazol-1-ylmethylphenyl)benzene-

30

## sulfonamide

<sup>1</sup>H NMR  $\delta$ (CDCl<sub>3</sub>): 8.95 (brs, 1H), 8.20 (d,  $J$  = 8.3 Hz, 1H), 7.66 (brs, 1H), 7.38 (d,  $J$  = 8.0 Hz, 2H), 7.34 (dd,  $J$  = 8.3, 1.6 Hz, 1H), 7.11 (d,  $J$  = 8.0 Hz, 2H), 7.05 (d,  $J$  = 1.6 Hz, 1H), 6.83 (brs, 2H), 5.10 (s, 2H), 4.00 (t,  $J$  = 6.5, 2H), 2.67 (t,  $J$  = 7.5 Hz, 2H), 1.62 (m, 2H), 1.48 (m, 2H), 1.36 (m, 2H), 1.22 (m, 2H), 0.92 (t,  $J$  = 7.2 Hz, 3H), 0.86 (t,  $J$  = 7.3 Hz, 3H)

<sup>13</sup>C NMR  $\delta$ (CDCl<sub>3</sub>): 151.9, 148.5, 140.2, 139.9, 136.7, 135.1, 134.7, 132.3, 130.8, 129.9, 127.7, 127.2, 126.9, 119.2, 65.9, 50.9, 35.4, 33.0, 30.5, 22.4, 18.8, 13.8, 13.6

- 10 (ii) *N*-(2-methoxyethyloxy)carbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide

<sup>1</sup>H NMR  $\delta$ (20% CD<sub>3</sub>OD in CDCl<sub>3</sub>): 8.00 (brs, 1H), 7.56 (d,  $J$  = 7.7 Hz, 2H), 7.19 (d,  $J$  = 7.7 Hz, 2H), 7.07 (brs, 2H), 6.75 (s, 1H), 5.20 (s, 2H), 4.14 (brt,  $J$  = 4.5 Hz, 2H), 3.52 (brt,  $J$  = 6.9 Hz, 2H), 3.32 (s, 3H), 2.70 (d,  $J$  = 7.1 Hz, 2H), 1.94 (m, 1H), 0.99 (d,  $J$  = 6.4 Hz, 6H)

<sup>13</sup>C NMR  $\delta$ (20% CD<sub>3</sub>OD in CDCl<sub>3</sub>): 153.1, 149.7, 144.0, 136.1, 134.8, 134.6, 132.8, 129.6, 128.8, 127.0, 125.6, 119.8, 70.0, 64.1, 58.2, 50.9, 38.9, 30.2, 21.8

- 20 (iii) *N*-ethyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide

<sup>1</sup>H NMR  $\delta$ (20% CD<sub>3</sub>OD in CDCl<sub>3</sub>): 7.78 (brs, 1H), 7.55 (d,  $J$  = 7.8 Hz, 2H), 7.24 (d,  $J$  = 7.8 Hz, 2H), 7.07 (brs, 2H), 6.77 (s, 1H), 5.22 (s, 2H), 4.06 (q,  $J$  = 7.1 Hz, 2H), 2.71 (d,  $J$  = 7.1 Hz, 2H), 1.95 (m, 1H), 1.17 (t,  $J$  = 7.1 Hz, 3H), 0.99 (d,  $J$  = 6.4 Hz, 6H)

25 <sup>13</sup>C NMR  $\delta$  (20% CD<sub>3</sub>OD in CDCl<sub>3</sub>): 153.0, 150.7, 145.1, 137.2, 135.9, 135.0, 132.7, 130.1, 129.5, 127.9, 127.6, 120.2, 62.6, 49.6, 39.5, 30.8, 22.3, 14.3

- (iv) *N*-*tert*-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide

$^1\text{H}$  NMR  $\delta$ (10%  $\text{CD}_3\text{OD}$  in  $\text{CDCl}_3$ ): 7.65 (brs, 1H), 7.39 (d,  $J = 7.9$  Hz, 2H), 7.11 (d,  $J = 7.9$  Hz, 2H), 6.94 (brs, 2H), 6.65 (s, 1H), 5.09 (s, 2H), 2.59 (d,  $J = 7.1$  Hz, 2H), 1.82 (m, 1H), 1.22 (s, 9H), 0.87 (d,  $J = 6.6$  Hz, 6H)

$^{13}\text{C}$  NMR  $\delta$ (10%  $\text{CD}_3\text{OD}$  in  $\text{CDCl}_3$ ): 150.5, 149.5, 144.6, 136.6, 135.5,  
5 134.2, 131.7, 129.5, 129.0, 128.0, 127.1, 119.6, 83.0, 50.6, 39.0, 30.3, 27.5, 21.9

(v) *N*-butyloxycarbonyl-3-[4-(4-methylimidazol-1-ylmethyl)phenyl]-5-  
*iso*-butylthiophene-2-sulfonamide

$^1\text{H}$  NMR  $\delta$ ( $\text{CDCl}_3$ ): 8.22 (s, 1H), 7.55 (d,  $J = 8.2$  Hz, 2H), 7.27 (d,  $J = 7.9$   
10 Hz, 2H), 6.84 (s, 1H), 6.74 (s, 1H), 5.18 (s, 2H), 4.03 (t,  $J = 6.6$  Hz, 2H), 2.71 (d,  $J = 6.9$  Hz, 2H), 2.24 (s, 3H), 1.94 (m, 1H), 1.51 (m, 2H), 1.28 (m, 2H), 1.00 (d,  $J = 6.6$  Hz, 6H), 0.87 (t,  $J = 7.4$  Hz, 3H)

$^{13}\text{C}$  NMR  $\delta$ ( $\text{CDCl}_3$ ): 152.4, 150.5, 144.6, 135.2, 134.5, 132.6, 130.0, 129.1,  
127.8, 117.1, 116.9, 66.3, 51.7, 39.3, 30.6, 22.3, 18.9, 13.6, 11.5

15 (vi) *N*-butyloxycarbonyl-3-(4-pyrazol-1-ylmethylphenyl)-5-*iso*-butyl-  
thiophene-2-sulfonamide

$^1\text{H}$  NMR  $\delta$ ( $\text{CDCl}_3$ ): 0.84 (t,  $J = 7.3$  Hz, 3H), 0.95 (d,  $J = 6.6$  Hz, 6H), 1.22  
(m, 2H), 1.48 (m, 2H), 1.90 (m, 1H), 2.66 (d,  $J = 6.9$  Hz, 2H), 4.01 (t,  $J =$   
6.6 Hz, 2H), 5.26 (s, 2H), 6.23 (s, 1H), 6.69 (s, 1H), 7.02 (d,  $J = 8.3$  Hz,  
20 2H), 7.37 (m, 3H), 7.48 (s, 1H)

$^{13}\text{C}$  NMR  $\delta$ ( $\text{CDCl}_3$ ): 13.6, 18.7, 22.2, 30.4, 39.2, 55.1, 66.5, 106.0, 127.3,  
129.3, 129.6, 133.7, 136.9, 139.4, 145.7, 150.6, 151.3

(vii) *N*-butyloxycarbonyl-3-[4-(3-trifluoromethylpyrazol-1-ylmethyl)-  
phenyl]-5-*iso*-butylthiophene-2-sulfonamide

25  $^1\text{H}$  NMR  $\delta$ ( $\text{CDCl}_3$ ): 7.66 (s, 1H), 7.50 (s, 1H), 7.42 (d,  $J = 8.1$  Hz, 2H), 7.23  
(d,  $J = 8.2$  Hz, 2H), 6.74 (s, 1H), 6.59 (d,  $J = 2.1$  Hz, 1H), 5.40 (s, 2H), 4.03  
(t,  $J = 6.6$  Hz, 2H), 2.71 (d,  $J = 6.9$  Hz, 2H), 1.96 (m, 1H), 1.49 (m, 2H),  
1.25 (m, 2H), 0.99 (d,  $J = 6.6$  Hz, 6H), 0.87 (t,  $J = 7.4$  Hz, 3H)

$^{13}\text{C}$  NMR  $\delta(\text{CDCl}_3)$ : 151.8, 150.2, 146.0, 143.6, 142.5, 141.8, 139.4, 136.0, 134.0, 131.1, 130.6, 129.4, 127.5, 123.2, 119.2, 66.9, 56.1, 39.3, 30.5, 22.2, 18.7, 13.5

(viii) *N*-(*N*-butyl-*N*-methyldamino)carbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide

$^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$ : 8.18 (brs, 1H), 7.84 (brs, 1H), 7.46 (d,  $J = 8.2$  Hz, 2H), 7.16 (d,  $J = 8.2$  Hz, 2H), 7.06 (brs, 1H), 6.99 (brs, 1H), 6.68 (s, 1H), 3.07 (brt, 2H), 2.67 (d,  $J = 7.1$  Hz, 2H), 2.56 (brs, 3H), 1.91 (m, 1H), 1.35 (m, 2H), 1.19 (m, 2H), 0.96 (d,  $J = 6.6$  Hz, 6H), 0.84 (t,  $J = 7.2$  Hz, 3H)

$^{13}\text{C}$  NMR  $\delta(\text{CDCl}_3)$ : 153.6, 149.8, 143.3, 136.9, 135.5, 135.1, 134.2, 129.6, 128.7, 127.2, 126.8, 119.8, 51.0, 48.5, 39.3, 34.3, 30.4, 29.7, 22.3, 19.8, 13.8

(ix) *N*-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-(2-methoxyethyl)thiophene-2-sulfonamide

$^1\text{H}$  NMR  $\delta(5\% \text{CD}_3\text{OD in CDCl}_3)$ : 7.86 (brs, 1H), 7.51 (d,  $J = 7.9$  Hz, 2H), 7.18 (d,  $J = 7.9$  Hz, 2H), 7.05 (brs, 1H), 6.99 (brs, 1H), 6.83 (s, 1H), 5.18 (s, 2H), 4.03 (t,  $J = 6.5$  Hz, 2H), 3.67 (t,  $J = 6.2$  Hz, 2H), 3.10 (t,  $J = 6.2$  Hz, 2H), 1.52 (m, 2H), 1.26 (m, 2H), 0.88 (t,  $J = 7.3$  Hz, 3H)

$^{13}\text{C}$  NMR  $\delta(5\% \text{CD}_3\text{OD in CDCl}_3)$ : 151.7, 148.1, 144.7, 136.9, 135.2, 134.8, 133.0, 129.9, 129.4, 127.4, 127.2, 119.8, 72.0, 66.3, 58.8, 51.1, 30.7, 30.5, 18.8, 13.6

#### Example 14

Title compounds of the Examples were tested in Tests A and B above and were found to exhibit an affinity for AT2 receptors of less than  $K_i = 100$  nM (e.g. less than 50 nM) and an affinity to AT1 receptors of more than  $K_i = 500$  nM (e.g. more than 1  $\mu\text{M}$ ).



Example 15

Title compounds of the Examples were tested in Test C above and were found to stimulate markedly mucosal alkalisation. This effect was blocked by co-administration of the selective AT<sub>2</sub> receptor antagonist PD123319  
5 (Sigma Chemical Company).